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MULTISCALE ANALYSIS AND SIMULATION OF A SIGNALLING PROCESS WITH SURFACE DIFFUSION *

MARIYA PTASHNYK[†] AND CHANDRASEKHAR VENKATARAMAN[‡]

Abstract. We present and analyse a model for cell signalling processes in biological tissues. The model includes diffusion and nonlinear reactions on the cell surfaces, and both inter- and intracellular signalling. Using techniques from the theory of two-scale convergence as well the unfolding method, we show convergence of the solutions to the model to solutions of a two-scale macroscopic problem. We also present a two-scale bulk-surface finite element method for the approximation of the macroscopic model. We report on some benchmarking results as well as numerical simulations in a biologically relevant regime that illustrate the influence of cell-scale heterogeneities on macroscopic concentrations.

Key words. Intercellular signalling, receptor-ligand interactions, homogenisation, nonlinear parabolic equations, surface diffusion, bulk-surface problems, surface finite elements

AMS subject classifications. 35B27, 35Kxx, 65M60

1. Introduction. Interactions between cells and the response of cells to external stimuli are largely regulated by intracellular signalling processes which are themselves activated by interactions between cell membrane receptors and signalling molecules (ligands) diffusing in the extracellular space. Consequently, receptor-ligand interactions and the activation of intracellular signalling pathways are involved in many important biological processes such as the immune response, cell movement and division, tissue development and homeostasis or repair, e.g., [1, 27, 41]. The complexity of the biochemistry involved in signalling networks, necessitates an integrated approach combining theoretical and computational studies with experimental and modelling efforts to further our understanding of cell signalling. Motivated by this need, in this work, we consider the modelling and analysis of signalling processes in biological tissues. Specifically, we are interested in modelling both the cell scale phenomena of receptor binding and cell signalling along with the tissue level dynamics of the ligands.

Mathematical modelling and analysis of signalling processes involving receptor-ligand interactions and GTPase (protein) molecules for a single cell was considered in a number of recent works, for example [7, 14, 45]. The majority of modelling studies to date in the literature focus only on phenomena at the scale of a single cell or simply naively ‘average out’ the cell scale dependence for tissue level modelling [36, 40, 46, 52]. However, the spatial separation between ligands diffusing in the intercellular space and receptors restricted to the cell membrane could be important even in tissue level models as shown, for example, in [24, 39] where it is crucial to ensuring robust branching in models for morphogenesis in organogenesis (e.g., in the formation of the lungs or the kidney). The heterogeneity in the interactions between ligands and receptors on the cell membrane given by receptor clustering on cell membranes [21, 50, 53] and/or lipid rafts [6, 19, 48] is also important for intercellular signalling processes. Similarly, in the mathematical and computational modelling of chemotaxis, cell polarisation through the clustering of receptors at the leading edge and gradients in the macroscopic ligand field generated by the binding of

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these receptors appear crucial to successful migration [15, 33, 34]. Thus microscopic modelling of receptor-ligand-based intercellular signalling processes in which both cell and tissue scale phenomena are accounted for is essential for a better understanding of biological systems.

In this work we consider the multiscale modelling and analysis of signalling processes in biological tissues. Starting from a microscopic description consisting of coupled bulk-surface systems of partial differential equations (PDEs) posed in a domain consisting of cells and the extra cellular space, we will derive a macroscopic two-scale model as the number of cells tends to infinity. In contrast to previous models for receptor-based signalling processes in biological tissues [37], we consider diffusion of membrane resident species on the cell surface and we also extend previous models by considering interactions between receptors and co-receptors on the cell membrane leading to activation of intracellular signalling processes. Furthermore, we propose a robust and efficient numerical method for the approximation of the macroscopic two-scale problem and apply it in a biologically relevant parameter regime.

The main difficulty in the multiscale analysis of the microscopic problem considered here is the strong nonlinearity of reaction terms coupled with surface diffusion and the dependence on a small parameter, corresponding to the size of the microstructure. This requires a rather delicate analysis and a new approach in the derivation of a priori estimates. We employ the trace and Gagliardo-Nirenberg inequalities together with an iteration processes to show the a priori estimates and boundedness of the solutions of the model equations. Similar ideas were used in [7] to show the well-posedness of a system describing nonlinear ligand-receptor interactions for a single cell, whose shape is evolving in time. However due to the multiscale nature and the corresponding scaling in the microscopic equations, the techniques from [7] cannot be applied directly to obtain uniform a priori estimates for the solutions of our microscopic model. To overcome this difficulty we use the structure of the nonlinear reaction terms and the periodic unfolding operator [10, 11, 20].

The bulk-surface coupling in the homogenised model induces some challenges in the design of a two-scale numerical scheme. For the numerical approximation of the macroscopic two-scale system we employ a two-scale bulk-surface finite element method. Bulk-surface finite element methods have been used in a number of recent studies for the approximation of coupled bulk-surface systems of elliptic and parabolic equations, including those modelling receptor-ligand interactions [13, 32, 35, 45], however to the best of the authors knowledge all such works have focussed on interactions at the scale of a single cell. Coupling the bulk-surface finite element approach with a two-scale finite element method [42], we are able to treat the approximation of the full macroscopic two-scale system and hence provide, as far as we are aware, the first work in which tissue level models for receptor-ligand interaction are simulated where receptor binding, unbinding and transport as well as cell signalling are taken into account at the cell scale. In order to validate the method we perform some benchmark tests to investigate the convergence of the method. We then propose and simulate a macroscopic two-scale cell signalling model in a biologically relevant regime. Our results illustrate the influence of the cell shape on the transport of macroscopic species as well as spatial heterogeneities at the cell-scale and their influence on tissue level behaviour. We focus on incorporating the single cell model within a generic cell signalling process outlined in [18] into our multiscale modelling framework. However we note that the majority of signalling pathways that are described in the literature lie within the general model framework considered in this work. For example, GTPase (e.g. Rho) and GPCR (G-protein coupled receptors) related signalling pathways

[29], uPAR-mediated signalling processes in human tissue [28] and Brassinosteroid hormone mediated signalling in plant cells [12].

The remainder of this paper is organised as follows. In Section 2 we derive our microscopic model for cell-signalling processes consisting of coupled bulk-surface systems of PDEs. In Section 3 we prove existence and uniqueness results and derive some a priori estimates for solutions of the microscopic model. Convergence results in the limit as the number of cells tends to infinity and the resultant macroscopic two-scale model equations satisfied by the limiting solutions are presented in Section 4. In Section 5 we formulate a numerical scheme for the approximation of the macroscopic two-scale model. We benchmark the convergence of the scheme in Section 6 and in Section 7 we apply the numerical method to the approximation of a biological example of a GTPase signalling network taking parameter values from previous studies. The definitions and main properties of the two-scale convergence and the unfolding method as well as some technical calculations for the proof of the boundedness of a solution of the microscopic model are summarised in the Appendix.

2. Microscopic model. In this section we present a derivation of a microscopic mathematical model for signalling processes in biological tissues. We consider a Lipschitz domain $\Omega \subset \mathbb{R}^d$, with $d = 2, 3$, representing a part of a biological tissue and assume a periodic distribution of cells in the tissue. To describe the microscopic structure of the tissue, given by extra- and intracellular spaces separated by cell membranes, we consider a ‘unit cell’ $Y = [0, 1]^d$, and the subdomains $\bar{Y}_i \subset Y$ and $Y_e = Y \setminus Y_i$, together with the boundary $\Gamma = \partial Y_i$. The domain occupied by the intracellular space is given by $\Omega_i^\varepsilon = \bigcup_{\xi \in \Xi^\varepsilon} \varepsilon(Y_i + \xi)$, where $\Xi^\varepsilon = \{\xi \in \mathbb{Z}^d, \varepsilon(Y_i + \xi) \subset \Omega\}$, and the extracellular space is denoted by $\Omega_e^\varepsilon = \Omega \setminus \bar{\Omega}_i^\varepsilon$. The surfaces that describe cell membranes are denoted by $\Gamma^\varepsilon = \bigcup_{\xi \in \Xi^\varepsilon} \varepsilon(\Gamma + \xi)$, see Figure 1 for a sketch of the geometry.

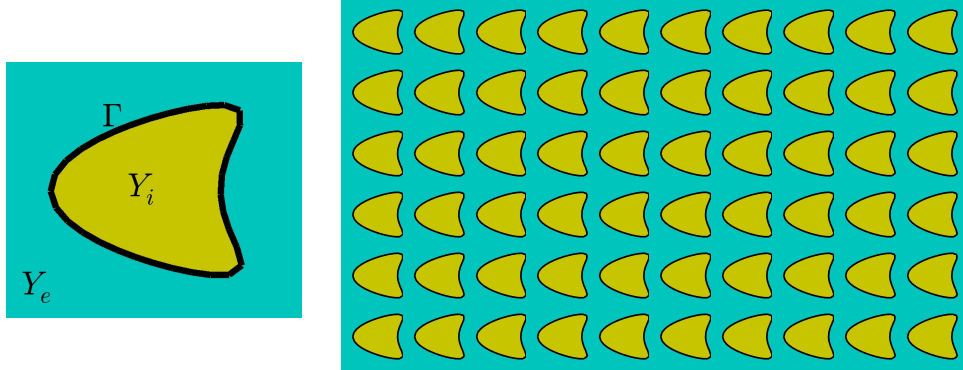


Fig. 1: The left hand subfigure shows the ‘unit cell’ that describes the microstructure consisting of a single cell with the intra- and extracellular spaces denoted by Y_i and Y_e respectively and the cell membrane by Γ . The right hand subfigure is a sketch of the tissue consisting of a periodic distribution of identically shaped cells surrounded by the extracellular space.

In modelling intercellular signalling processes, we assume that the signalling molecules (ligands) c_e^ε diffuse in the extracellular space and interact with cell membrane receptors. We distinguish between free receptors r_f^ε (or extracellular domains

of the free receptors) and bound receptors r_b^ε (free receptor-ligand complexes). The model for the evolution of the ligand concentration c_e^ε in the extracellular space Ω_e^ε reads

$$(2.1) \quad \begin{aligned} \partial_t c_e^\varepsilon - \nabla \cdot (D_e^\varepsilon(x) \nabla c_e^\varepsilon) &= F_e(c_e^\varepsilon) & \text{in } \Omega_e^\varepsilon, t > 0, \\ D_e^\varepsilon(x) \nabla c_e^\varepsilon \cdot \nu &= -\varepsilon G_e(c_e^\varepsilon, r_f^\varepsilon, r_b^\varepsilon) & \text{on } \Gamma^\varepsilon, t > 0. \end{aligned}$$

Here the nonlinear Robin boundary condition $G_e(c_e^\varepsilon, r_f^\varepsilon, r_b^\varepsilon)$ defined by

$$G_e(u, v, w) := a_e^\varepsilon(x) u v - b_e^\varepsilon(x) w,$$

describes the binding of ligands to free receptors located on the cell membranes, i.e., the creation of receptor-ligand complexes, with binding rate a_e^ε and spontaneous dissociation of the complexes back into free receptors and ligands, with dissociation rate b_e^ε . The function F_e models the production and/or decay of ligands in the extracellular space.

The signal from the extracellular domain is transduced into the cell through the activation by bound receptors r_b^ε of either membrane proteins, as is the case in signalling processes mediated by G-protein-coupled receptors, or, the intracellular domains of enzyme-linked membrane receptors or co-receptors, as observed in plant hormone signalling processes. Thus we shall distinguish between active p_a^ε and inactive p_d^ε proteins (co-receptors) or active and inactive intracellular domains of receptors. We also consider spontaneous deactivation of proteins (or intracellular domains of receptors) with the deactivation rate b_i^ε , as well as natural decay of all molecules with decay rates d_j , for $j = f, e, d, a$. Hence for the receptors and proteins on the cell membrane we obtain the following reaction-diffusion equations

$$(2.2) \quad \begin{aligned} \partial_t r_f^\varepsilon - \varepsilon^2 D_f \Delta_\Gamma r_f^\varepsilon &= F_f(r_f^\varepsilon, r_b^\varepsilon) - G_e(c_e^\varepsilon, r_f^\varepsilon, r_b^\varepsilon) - d_f r_f^\varepsilon & \text{on } \Gamma^\varepsilon, t > 0, \\ \partial_t r_b^\varepsilon - \varepsilon^2 D_b \Delta_\Gamma r_b^\varepsilon &= G_e(c_e^\varepsilon, r_f^\varepsilon, r_b^\varepsilon) - G_d(r_b^\varepsilon, p_d^\varepsilon, p_a^\varepsilon) - d_b r_b^\varepsilon & \text{on } \Gamma^\varepsilon, t > 0, \\ \partial_t p_d^\varepsilon - \varepsilon^2 D_d \Delta_\Gamma p_d^\varepsilon &= F_d(p_d^\varepsilon) - G_d(r_b^\varepsilon, p_d^\varepsilon, p_a^\varepsilon) - d_d p_d^\varepsilon & \text{on } \Gamma^\varepsilon, t > 0, \\ \partial_t p_a^\varepsilon - \varepsilon^2 D_a \Delta_\Gamma p_a^\varepsilon &= G_d(r_b^\varepsilon, p_d^\varepsilon, p_a^\varepsilon) - G_i(p_a^\varepsilon, c_i^\varepsilon) - d_a p_a^\varepsilon & \text{on } \Gamma^\varepsilon, t > 0, \end{aligned}$$

where Δ_Γ denotes the Laplace-Beltrami operator on the surfaces Γ^ε and the activation/deactivation reactions are defined by

$$G_d(u, v, w) := a_i^\varepsilon(x) u v - b_i^\varepsilon(x) w,$$

with an activation (binding) rate a_i^ε . The function

$$G_i(w, v) := \gamma_i^\varepsilon(x) w - \kappa_i^\varepsilon(x) v$$

describes the transduction of the signal into the cell interior by activated proteins on the cell membrane (GTPase molecules) or activated intracellular domains of enzyme-linked receptors. The functions F_f and F_d model the production of new free receptors and inactive proteins, respectively.

For the molecules involved in the intracellular part of the signalling pathway, we consider

$$(2.3) \quad \begin{aligned} \partial_t c_i^\varepsilon - \varepsilon^2 \nabla \cdot (D_i^\varepsilon(x) \nabla c_i^\varepsilon) &= F_i(c_i^\varepsilon) & \text{in } \Omega_i^\varepsilon, t > 0, \\ \varepsilon^2 D_i^\varepsilon(x) \nabla c_i^\varepsilon \cdot \nu &= \varepsilon G_i(p_a^\varepsilon, c_i^\varepsilon) & \text{on } \Gamma^\varepsilon, t > 0, \end{aligned}$$

where the function F_i models production and/or decay of the intracellular signalling molecules c_i^ε .

We complete the microscopic model with the initial conditions

$$(2.4) \quad \begin{aligned} c_e^\varepsilon(0, x) &= c_{e,0}(x) && \text{for } x \in \Omega_e^\varepsilon, \\ c_i^\varepsilon(0, x) &= c_{i,0}^\varepsilon(x), \quad c_{i,0}^\varepsilon(x) = c_{i,1}(x)c_{i,2}(x/\varepsilon) && \text{for } x \in \Omega_i^\varepsilon, \\ r_j^\varepsilon(0, x) &= r_{j,0}^\varepsilon(x), \quad r_{j,0}^\varepsilon(x) = r_{j,1}(x)r_{j,2}(x/\varepsilon) && \text{for } x \in \Gamma^\varepsilon, \\ p_s^\varepsilon(0, x) &= p_{s,0}^\varepsilon(x), \quad p_{s,0}^\varepsilon(x) = p_{s,1}(x)p_{s,2}(x/\varepsilon) && \text{for } x \in \Gamma^\varepsilon, \end{aligned}$$

where $j = f, b$, and $s = d, a$, and the boundary condition for c_e^ε on the external boundary $\partial\Omega$ is given by,

$$(2.5) \quad D_e^\varepsilon(x) \nabla c_e^\varepsilon \cdot \nu = 0 \quad \text{on } \partial\Omega, \quad t > 0.$$

Remark 2.1 (Modelling generalisations). For simplicity of presentation we consider constant diffusion coefficients in the equations on Γ^ε , however both the mathematical analysis and the numerical implementation allow for general space dependence (x and/or x/ε) in the diffusion coefficients.

The ε -dependent scaling in the microscopic model (2.1)–(2.5) yields nontrivial equations in the limit and indeed is consistent with biological estimates of the parameter values c.f., Section 7.

The structure of space-dependent initial conditions ensures the uniform in ε boundedness and strong two-scale convergence of the initial data $c_{i,0}^\varepsilon$, $r_{j,0}^\varepsilon$, and $p_{s,0}^\varepsilon$ as $\varepsilon \rightarrow 0$, where $j = f, b$ and $s = d, a$. It is possible to consider more general initial conditions, i.e. $c_{i,0}^\varepsilon(x) = c_{i,0}(x, x/\varepsilon)$, $r_{j,0}^\varepsilon(x) = r_{j,0}(x, x/\varepsilon)$, and $p_{s,0}^\varepsilon(x) = p_{s,0}(x, x/\varepsilon)$ if one assumes continuity of $c_{i,0}$, $r_{j,0}$, and $p_{s,0}$ with respect to at least one of the spatial variables, i.e., macroscopic ($x \in \Omega$) or microscopic ($y \in Y_i$ or $y \in \Gamma$).

Remark 2.2 (Binding kinetics). For reasons of clarity of exposition in the microscopic model we consider linear or quadratic reactions for interactions between signalling molecules, receptors and proteins. Such reactions capture the main features of the biologically relevant interactions. The extension of the analysis and numerical simulations considered here to more general binding models such as cooperative binding or Michaelis-Menten terms and the addition of general Lipschitz functions in the reaction terms modelling additional phenomena should be a relatively straightforward task and is not anticipated to induce any major technical complications.

To ease readability, we introduce the following notation for $\tau \in (0, T]$ and any $T > 0$, $\Omega_{l,\tau}^\varepsilon := (0, \tau) \times \Omega_l^\varepsilon$, for $l = e, i$, $\Gamma_\tau^\varepsilon := (0, \tau) \times \Gamma^\varepsilon$, $\Omega_\tau := \Omega \times (0, \tau)$, $\Gamma_\tau := \Gamma \times (0, \tau)$,

$$\begin{aligned} \langle \phi, \psi \rangle_{\Omega_{l,\tau}^\varepsilon} &:= \int_0^\tau \int_{\Omega_l^\varepsilon} \phi \psi \, dx dt, \quad \text{for } l = e, i, & \langle \phi, \psi \rangle_{\Gamma_\tau^\varepsilon} &:= \int_0^\tau \int_{\Gamma^\varepsilon} \phi \psi \, d\sigma^\varepsilon dt, \\ \langle \phi, \psi \rangle_{Y_i \times \Omega_\tau} &:= \int_0^\tau \int_{\Omega} \int_{Y_i} \phi \psi \, dy dx dt, \quad \text{for } l = e, i, & \langle \phi, \psi \rangle_{\Omega_\tau} &:= \int_0^\tau \int_{\Omega} \phi \psi \, dx dt, \\ \langle \phi, \psi \rangle_{\Gamma \times \Omega_\tau} &:= \int_0^\tau \int_{\Omega} \int_{\Gamma} \phi \psi \, d\sigma_y dx dt, & \langle \phi, \psi \rangle_{\Gamma_\tau} &:= \int_0^\tau \int_{\Gamma} \phi \psi \, d\sigma_y dt. \end{aligned}$$

By $\langle \cdot, \cdot \rangle$ we denote the dual product in $H^1(\Omega_l^\varepsilon)$, with $l = i, e$, or in $H^1(\Gamma^\varepsilon)$ where it is clear from the arguments which of the three is meant.

3. Well posedness and a priori estimates for the microscopic model.

In this section, we prove existence and uniqueness of a solution to the microscopic problem (2.1)–(2.5). We also derive a priori estimates that allow us to pass to the limit as the number of cells tends to infinity.

We use a Galerkin method together with fixed point arguments to show the existence of a weak solution of (2.1)–(2.5). The main difficulty in the analysis is to show a priori estimates for solutions of the microscopic problem, which are global in time and independent of ε . This is technically challenging due to the quadratic nonlinearities in the reaction terms and the scaling of the diffusion of the microscopic species. The tools we use to derive the estimates are the periodic unfolding method, Gagliardo-Nirenberg inequalities and in the proof of boundedness of the species, we employ an Alikakos iteration technique [3]. Uniqueness of the solution to (2.1)–(2.5) follows from the boundedness result and the local Lipschitz continuity of the nonlinear terms.

We find it convenient to use the periodic unfolding method described in Appendix B, see also [10, 11]. There are two main advantages in using unfolding methods in relation to the present study:

- Unfolding operators map functions defined on the oscillating ε -dependent domains to functions defined on fixed domains which now depend on both macroscopic and microscopic variables; i.e., we can study functions on fixed domains whose geometry is independent of ε but in exchange must double the spatial dimension.
- The unfolding results in a separation between microscopic and macroscopic variables in the unfolded functions. This allows us to take advantage of the fact that under the action of the unfolding operator the differential operator (the Laplace-Beltrami operator) in the equations defined on the oscillating surfaces is transformed into a differential operator with respect to the microscopic variables only. Thus we are able to utilise the higher regularity with respect to microscopic variables of the species defined on the oscillating surfaces and this appears to be crucial in establishing boundedness of the species uniformly in ε .

We make the following biologically reasonable assumptions on the coefficients in the model equations and on the initial data.

Assumption 3.1 (Assumptions on the problem data for (2.1)–(2.5)).

- We assume the usual ellipticity and boundedness conditions on the diffusivities of the different species, i.e., $D_e \in C(\bar{\Omega}; L^\infty(Y_e))$, with $D_e(x, y) \geq \alpha_e > 0$ for a.a. $y \in Y_e$ and $x \in \Omega$, $D_i \in L^\infty(Y_i)$ with $D_i(y) \geq \alpha_i > 0$ for a.a. $y \in Y_i$, and $D_j > 0$, for $j = f, b, d, a$.
- For the reaction kinetic coefficients, for $l = e, i$, we assume

$$a_l, b_l, \gamma_i, \kappa_i \in L^\infty(\Gamma) \text{ and } a_l, b_l, \gamma_i, \kappa_i \text{ are nonnegative.}$$

Moreover, we assume for $l = e, i$

$$a_l^\varepsilon(x) = a_l(x/\varepsilon), b_l^\varepsilon(x) = b_l(x/\varepsilon) \text{ and } \gamma_i^\varepsilon(x) = \gamma_i(x/\varepsilon), \kappa_i^\varepsilon(x) = \kappa_i(x/\varepsilon).$$

- We assume boundedness of the initial conditions, i.e.,

$$c_{e,0}, c_{i,1} \in L^\infty(\Omega) \text{ and } c_{i,2} \in L^\infty(Y),$$

and that for $j = f, b$ and $s = a, d$,

$$r_{j,1}, p_{s,1} \in L^\infty(\Omega) \text{ and } r_{j,2}, p_{s,2} \in L^\infty(\Gamma).$$

- We further assume that the production/decay terms satisfy, $F_l : \mathbb{R} \rightarrow \mathbb{R}$, for $l = e, i, d$, and $F_f : \mathbb{R}^2 \rightarrow \mathbb{R}$ are locally Lipschitz continuous in $(-\mu, \infty)$ and $(-\mu, \infty)^2$, respectively, for some $\mu > 0$.

Moreover, we assume the following growth bounds, for $l = e, i, d$

$$F_l(\xi)\xi_- \leq |\xi_-|^2 \text{ and } F_f(\xi, \eta)\xi_- \leq C(|\xi_-|^2 + |\eta_-|^2),$$

for $\xi_- = \min\{\xi, 0\}$ and $\eta_- = \min\{\eta, 0\}$, and for $l = e, i, d$

$$|F_l(\xi)| \leq C(1 + \xi) \text{ and } |F_f(\xi, \eta)| \leq C(1 + \xi + \eta) \text{ for } \xi, \eta \in \mathbb{R}_+.$$

We define $D_i^\varepsilon(x) := \tilde{D}_i(x/\varepsilon)$ and $D_e^\varepsilon(x) := \tilde{D}_e(x, x/\varepsilon)$ for $x \in \Omega$, where \tilde{D}_i and \tilde{D}_e are Y -periodic extensions of D_i and of $D_e(x, \cdot)$ for $x \in \bar{\Omega}$, respectively.

We now introduce our notion of weak solutions of the microscopic problem (2.1)–(2.5).

DEFINITION 3.2 (Weak solution of the microscopic problem). *A weak solution of the microscopic model (2.1)–(2.5) are functions $c_l^\varepsilon \in L^2(0, T; H^1(\Omega_l^\varepsilon))$ and $r_j^\varepsilon, p_s^\varepsilon \in L^2(0, T; H^1(\Gamma^\varepsilon))$, with $\partial_t c_l^\varepsilon \in L^2(0, T; H^1(\Omega_l^\varepsilon)')$ and $\partial_t r_j^\varepsilon, \partial_t p_s^\varepsilon \in L^2(0, T; H^1(\Gamma^\varepsilon)')$, for $l = e, i$, $s = a, d$, and $j = f, b$, satisfying*

$$(3.1) \quad \begin{aligned} \langle \partial_t c_e^\varepsilon, \phi \rangle + \langle D_e^\varepsilon(x) \nabla c_e^\varepsilon, \nabla \phi \rangle_{\Omega_{e,T}^\varepsilon} &= \langle F_e(c_e^\varepsilon), \phi \rangle_{\Omega_{e,T}^\varepsilon} - \varepsilon \langle G_e(c_e^\varepsilon, r_f^\varepsilon, r_b^\varepsilon), \phi \rangle_{\Gamma_T^\varepsilon}, \\ \langle \partial_t c_i^\varepsilon, \psi \rangle + \langle \varepsilon^2 D_i^\varepsilon(x) \nabla c_i^\varepsilon, \nabla \psi \rangle_{\Omega_{i,T}^\varepsilon} &= \langle F_i(c_i^\varepsilon), \psi \rangle_{\Omega_{i,T}^\varepsilon} + \varepsilon \langle G_i(p_a^\varepsilon, c_i^\varepsilon), \psi \rangle_{\Gamma_T^\varepsilon}, \end{aligned}$$

and

$$(3.2) \quad \begin{aligned} \langle \partial_t r_f^\varepsilon, \varphi \rangle + \langle \varepsilon^2 D_f \nabla_\Gamma r_f^\varepsilon, \nabla_\Gamma \varphi \rangle_{\Gamma_T^\varepsilon} &= \langle F_f(r_f^\varepsilon, r_b^\varepsilon) - G_e(c_e^\varepsilon, r_f^\varepsilon, r_b^\varepsilon) - d_f r_f^\varepsilon, \varphi \rangle_{\Gamma_T^\varepsilon}, \\ \langle \partial_t r_b^\varepsilon, \varphi \rangle + \langle \varepsilon^2 D_b \nabla_\Gamma r_b^\varepsilon, \nabla_\Gamma \varphi \rangle_{\Gamma_T^\varepsilon} &= \langle G_e(c_e^\varepsilon, r_f^\varepsilon, r_b^\varepsilon) - G_d(r_b^\varepsilon, p_d^\varepsilon, p_a^\varepsilon), \varphi \rangle_{\Gamma_T^\varepsilon} \\ &\quad - \langle d_b r_b^\varepsilon, \varphi \rangle_{\Gamma_T^\varepsilon}, \\ \langle \partial_t p_d^\varepsilon, \varphi \rangle + \langle \varepsilon^2 D_d \nabla_\Gamma p_d^\varepsilon, \nabla_\Gamma \varphi \rangle_{\Gamma_T^\varepsilon} &= \langle F_d(p_d^\varepsilon) - G_d(r_b^\varepsilon, p_d^\varepsilon, p_a^\varepsilon) - d_d p_d^\varepsilon, \varphi \rangle_{\Gamma_T^\varepsilon}, \\ \langle \partial_t p_a^\varepsilon, \varphi \rangle + \langle \varepsilon^2 D_a \nabla_\Gamma p_a^\varepsilon, \nabla_\Gamma \varphi \rangle_{\Gamma_T^\varepsilon} &= \langle G_d(r_b^\varepsilon, p_d^\varepsilon, p_a^\varepsilon) - G_i(p_a^\varepsilon, c_i^\varepsilon) - d_a p_a^\varepsilon, \varphi \rangle_{\Gamma_T^\varepsilon}, \end{aligned}$$

for all $\phi \in L^2(0, T; H^1(\Omega_e^\varepsilon))$, $\psi \in L^2(0, T; H^1(\Omega_i^\varepsilon))$, and $\varphi \in L^2(0, T; H^1(\Gamma^\varepsilon))$, with the initial conditions (2.4) satisfied in the L^2 -sense.

In the subsequent analysis we shall make repeated use of the the following scaled trace inequality.

Remark 3.3 (Scaled trace inequality). Using the assumptions on the microscopic geometry of Ω_l^ε and applying the standard trace inequality for functions $v \in H^1(Y_l)$, see e.g. (A.1), together with a scaling argument, we obtain the following trace inequality for the L^2 -norm on Γ^ε :

$$(3.3) \quad \varepsilon \|v\|_{L^2(\Gamma^\varepsilon)}^2 \leq \mu_\delta \|v\|_{L^2(\Omega_l^\varepsilon)}^2 + \varepsilon^2 \delta \|\nabla v\|_{L^2(\Omega_l^\varepsilon)}^2 \quad \text{with } l = e, i,$$

for any fixed $\delta > 0$, where the constant $\mu_\delta > 0$ depends only on δ , Y , Y_i and Γ , and is independent of ε , see e.g. [23, 37]. Notice that the natural ε -scaling in the L^2 -norm on the oscillating boundaries (surfaces of the microstructure) reflects the difference between volume and surface dimensions.

Remark 3.4 (H^1 extension). The assumptions on the structure of the microscopic domain Ω_e^ε ensure that for $v \in W^p(\Omega_e^\varepsilon)$, with $1 \leq p < \infty$, there exists an extension \bar{v} from Ω_e^ε into Ω such that

$$(3.4) \quad \|\bar{v}\|_{L^p(\Omega)} \leq \mu \|v\|_{L^p(\Omega_e^\varepsilon)}, \quad \|\nabla \bar{v}\|_{L^p(\Omega)} \leq \mu \|\nabla v\|_{L^p(\Omega_e^\varepsilon)},$$

where the constant μ is independent of ε , see e.g. [2, 9, 23].

We now state our main result of this section, specifically the existence and uniqueness of a weak solution of microscopic model (2.1)–(2.5) together with uniform (in ε) estimates.

THEOREM 3.5. *Under Assumption 3.1, for every fixed $\varepsilon > 0$, there exists a unique nonnegative weak solution of the microscopic problem (2.1)–(2.5), which satisfies the a priori estimates*

$$(3.5) \quad \begin{aligned} & \|c_e^\varepsilon\|_{L^\infty(0,T;L^2(\Omega_e^\varepsilon))} + \|\nabla c_e^\varepsilon\|_{L^2(\Omega_{e,T}^\varepsilon)} + \sqrt{\varepsilon}\|c_e^\varepsilon\|_{L^2(\Gamma_T^\varepsilon)} \leq C, \\ & \|c_i^\varepsilon\|_{L^\infty(0,T;L^2(\Omega_i^\varepsilon))} + \|\varepsilon \nabla c_i^\varepsilon\|_{L^2(\Omega_{i,T}^\varepsilon)} + \sqrt{\varepsilon}\|c_i^\varepsilon\|_{L^2(\Gamma_T^\varepsilon)} \leq C, \\ & \sqrt{\varepsilon}\|r_j^\varepsilon\|_{L^\infty(0,T;L^2(\Gamma^\varepsilon))} + \sqrt{\varepsilon}\|\varepsilon \nabla_\Gamma r_j^\varepsilon\|_{L^2(\Gamma_T^\varepsilon)} \leq C, \\ & \sqrt{\varepsilon}\|p_s^\varepsilon\|_{L^\infty(0,T;L^2(\Gamma^\varepsilon))} + \sqrt{\varepsilon}\|\varepsilon \nabla_\Gamma p_s^\varepsilon\|_{L^2(\Gamma_T^\varepsilon)} \leq C, \end{aligned}$$

and for $l = e, i$, $s = a, d$, and $j = f, b$

$$(3.6) \quad \|c_l^\varepsilon\|_{L^\infty(0,T;L^\infty(\Omega_l^\varepsilon))} + \|r_j^\varepsilon\|_{L^\infty(0,T;L^\infty(\Gamma^\varepsilon))} + \|p_s^\varepsilon\|_{L^\infty(0,T;L^\infty(\Gamma^\varepsilon))} \leq C,$$

where the constant C is independent of ε .

To aid readability, we split the proof of Theorem 3.5 into a series of Lemmas. Namely, in Lemmas 3.6, 3.7, 3.8, 3.9 and 3.10 we show existence, nonnegativity, the apriori estimates (3.5), boundedness and uniqueness of solutions to (2.1)–(2.5) respectively.

LEMMA 3.6. *There exists a weak solution to the microscopic problem (2.1)–(2.5).*

Proof. Existence of a weak solution to problem (2.1)–(2.5) is demonstrated by showing the existence of a fixed point of the operator equation $K : \mathcal{A} \rightarrow \mathcal{A}$, with

$$\mathcal{A} = \{(u, v) \in L^2(0, T; L^4(\Gamma^\varepsilon))^2, \text{ with } u \geq 0 \text{ and } v \geq 0 \text{ on } (0, T) \times \Gamma^\varepsilon\},$$

defined such that for given $(g^\varepsilon, h^\varepsilon) \in \mathcal{A}$ we consider $(r_f^\varepsilon, r_b^\varepsilon) = K(g^\varepsilon, h^\varepsilon)$, where the functions r_f^ε and r_b^ε are solutions of the following coupled problem

$$(3.7) \quad \begin{aligned} & \partial_t c_e^\varepsilon - \nabla \cdot (D_e^\varepsilon(x) \nabla c_e^\varepsilon) = F_e(c_e^\varepsilon) & \text{in } \Omega_{e,T}^\varepsilon, \\ & D_e^\varepsilon(x) \nabla c_e^\varepsilon \cdot \nu = -\varepsilon G_e(c_e^\varepsilon, g^\varepsilon, h^\varepsilon) & \text{on } \Gamma_T^\varepsilon, \\ & D_e^\varepsilon(x) \nabla c_e^\varepsilon \cdot \nu = 0 & \text{on } (\partial\Omega)_T, \\ & \partial_t c_i^\varepsilon - \varepsilon^2 \nabla \cdot (D_i^\varepsilon(x) \nabla c_i^\varepsilon) = F_i(c_i^\varepsilon) & \text{in } \Omega_{i,T}^\varepsilon, \\ & D_i^\varepsilon(x) \nabla c_i^\varepsilon \cdot \nu = \varepsilon G_i(p_a^\varepsilon, c_i^\varepsilon) & \text{on } \Gamma_T^\varepsilon, \end{aligned}$$

and

$$(3.8) \quad \begin{aligned} & \partial_t r_f^\varepsilon - \varepsilon^2 \nabla_\Gamma \cdot (D_f \nabla_\Gamma r_f^\varepsilon) = F_f(r_f^\varepsilon, h^\varepsilon) - G_e(c_e^\varepsilon, g^\varepsilon, r_b^\varepsilon) - d_f r_f^\varepsilon, \\ & \partial_t r_b^\varepsilon - \varepsilon^2 \nabla_\Gamma \cdot (D_b \nabla_\Gamma r_b^\varepsilon) = G_e(c_e^\varepsilon, g^\varepsilon, r_b^\varepsilon) - G_d(h^\varepsilon, p_d^\varepsilon, p_a^\varepsilon) - d_b r_b^\varepsilon, \\ & \partial_t p_d^\varepsilon - \varepsilon^2 \nabla_\Gamma \cdot (D_d \nabla_\Gamma p_d^\varepsilon) = F_d(p_d^\varepsilon) - G_d(h^\varepsilon, p_d^\varepsilon, p_a^\varepsilon) - d_d p_d^\varepsilon, \\ & \partial_t p_a^\varepsilon - \varepsilon^2 \nabla_\Gamma \cdot (D_a \nabla_\Gamma p_a^\varepsilon) = G_d(h^\varepsilon, p_d^\varepsilon, p_a^\varepsilon) - G_i(p_a^\varepsilon, c_i^\varepsilon) - d_a p_a^\varepsilon, \end{aligned}$$

together with the initial conditions (2.4).

To prove the nonnegativity of solutions of problem (3.7), (3.8), and (2.4) we start by taking $c_e^{\varepsilon,-} = \min\{c_e^\varepsilon, 0\}$ as a test function in the equation for c_e^ε in (3.7). Using the nonnegativity of g^ε and h^ε , the assumptions on F_e and the structure of function G_e

we obtain that $\|c_e^{\varepsilon,-}\|_{L^\infty(0,T;L^2(\Omega^\varepsilon))} \leq 0$. Hence $c_e^{\varepsilon,-} = 0$ a.e. in $(0,T) \times \Omega_e^\varepsilon$ and $c_e^\varepsilon \geq 0$ a.e. in $(0,T) \times \Omega_e^\varepsilon$. Then using the nonnegativity of c_e^ε , g^ε , and h^ε , and choosing $c_i^{\varepsilon,-}$, $r_l^{\varepsilon,-}$, $p_s^{\varepsilon,-}$, with $l = f, b$ and $s = a, d$, as test functions in the equation for c_i^ε in (3.7) and in equations in (3.8), respectively, and using the assumptions on the functions F_f , F_d , F_i , G_i and G_d we obtain nonnegativity of c_i^ε , r_l^ε , and p_s^ε , where $l = f, b$ and $s = a, d$.

The existence of a solution of problem (3.7), (3.8), and (2.4) for given $(g^\varepsilon, h^\varepsilon) \in \mathcal{A}$ can be shown using a Galerkin method and a priori estimates, equivalent to those stated in (3.5) (where we now consider estimates for the solutions of problem (3.7), (3.8), and (2.4)). As is standard the necessary estimates are derived for Galerkin approximation sequences and passing to the limit yields the estimates for the problem (3.7), (3.8), and (2.4). We note that the derivation of the estimates (3.5) for solutions of problem (3.7), (3.8), and (2.4) follows exactly the same argument as in the proof of Lemma 3.8, with $\varepsilon \|h^\varepsilon\|_{L^2(0,T;L^q(\Gamma^\varepsilon))}^2$ in place of $\varepsilon \|r_b^\varepsilon\|_{L^2(0,T;L^q(\Gamma^\varepsilon))}^2$ for $q = 2, 4$.

The a priori estimates in (3.5), together with standard arguments for parabolic equations, ensure that for any fixed $\varepsilon > 0$ we have $\partial_t c_l^\varepsilon \in L^2(0,T;H^1(\Omega_l^\varepsilon)')$ for $l = e, i$ and $\partial_t r_j^\varepsilon, \partial_t p_s^\varepsilon \in L^2(0,T;H^1(\Gamma^\varepsilon)')$ for $j = f, b, s = a, d$.

Now using the compact embedding of $[H^1(0,T;H^1(\Gamma^\varepsilon)') \cap L^2(0,T;H^1(\Gamma^\varepsilon))]^2$ in $L^2(0,T;L^4(\Gamma^\varepsilon))^2$ and the fact that \mathcal{A} is a convex subset of $L^2(0,T;L^4(\Gamma^\varepsilon))^2$ and applying the Schauder fixed-point theorem yields the existence of a weak solution to the microscopic problem (2.1)–(2.5) for each fixed ε . \square

To show nonnegativity of solutions, the a priori estimates (3.5) and boundedness of solutions of the microscopic problem (2.1)–(2.5), we first consider a truncated model obtained by taking $r_{f,M}^\varepsilon$ instead of r_f^ε in function G_e and $r_{b,M}^\varepsilon$ instead of r_b^ε in function G_d in equations (2.1)–(2.5), where

$$r_{j,M}^\varepsilon := \min\{M, r_j^\varepsilon\} + \max\{-M, r_j^\varepsilon\} - r_j^\varepsilon, \text{ for } j = f, b \text{ and some } M > 0.$$

Then we show that all solutions of the truncated model are nonnegative. For nonnegative solutions in Lemmata 3.8 and 3.9 we prove the a priori estimates (3.5) and boundedness, independent of the truncation constant M . Thus passing to the limit as $M \rightarrow \infty$ yields the nonnegativity, a priori estimates (3.5) and boundedness of solutions of the original problem (2.1)–(2.5).

For simplicity of presentation we derive the a priori estimates and boundedness of nonnegative solutions of original problem (2.1)–(2.5), clearly the same arguments apply for the corresponding truncated model.

LEMMA 3.7. *Under Assumptions 3.1 solutions of problem (2.1)–(2.5) are nonnegative.*

Proof. We first consider the truncated model with $r_{f,M}^\varepsilon$ instead of r_f^ε in function G_e and $r_{b,M}^\varepsilon$ instead of r_b^ε in function G_d in equations (2.1)–(2.5). Then considering $c_l^{\varepsilon,-}$, $r_j^{\varepsilon,-}$, and $p_s^{\varepsilon,-}$ as test functions in equations (3.1) and (3.2) with $G_e(c_e^\varepsilon, r_{f,M}^\varepsilon, r_b^\varepsilon)$ and $G_d(r_{b,M}^\varepsilon, p_d^\varepsilon, p_a^\varepsilon)$ instead of $G_e(c_e^\varepsilon, r_f^\varepsilon, r_b^\varepsilon)$ and $G_d(r_b^\varepsilon, p_d^\varepsilon, p_a^\varepsilon)$, respectively, using the trace and Gronwall inequalities we obtain

$$\|c_l^{\varepsilon,-}\|_{L^\infty(0,T;L^2(\Omega_l^\varepsilon))} + \|r_j^{\varepsilon,-}\|_{L^\infty(0,T;L^2(\Gamma^\varepsilon))} + \|p_s^{\varepsilon,-}\|_{L^\infty(0,T;L^2(\Gamma^\varepsilon))} \leq 0,$$

for $l = e, i$, $j = f, b$, and $s = a, d$, and hence solutions of the truncated problem c_l^ε , r_j^ε , and p_s^ε are nonnegative. Since for nonnegative solutions we have a priori estimates and boundedness uniformly with respect to M , see Lemmata 3.8 and 3.9, we can pass

to the limit as $M \rightarrow \infty$ and obtain that solutions of the original problem (2.1)–(2.5) are nonnegative. \square

Next we derive the a priori estimates (3.5) for solutions of problem (2.1)–(2.5).

LEMMA 3.8. *Under Assumptions 3.1 nonnegative solutions of the microscopic problem (2.1)–(2.5) satisfy the a priori estimates (3.5).*

Proof. Considering c_e^ε and c_i^ε as test functions in the weak formulation (3.1) of the equations for c_e^ε and c_i^ε yields

$$(3.9) \quad \begin{aligned} \frac{1}{2} \|c_e^\varepsilon(\tau)\|_{L^2(\Omega_\varepsilon)}^2 + \alpha_e \|\nabla c_e^\varepsilon\|_{L^2(\Omega_{\varepsilon,\tau}^\varepsilon)}^2 &\leq \frac{1}{2} \|c_e^\varepsilon(0)\|_{L^2(\Omega_\varepsilon)}^2 + \langle F_e(c_e^\varepsilon), c_e^\varepsilon \rangle_{\Omega_{\varepsilon,\tau}^\varepsilon} \\ &\quad - \varepsilon \langle G_e(c_e^\varepsilon, r_f^\varepsilon, r_b^\varepsilon), c_e^\varepsilon \rangle_{\Gamma_\tau^\varepsilon}, \\ \frac{1}{2} \|c_i^\varepsilon(\tau)\|_{L^2(\Omega_i^\varepsilon)}^2 + \alpha_i \|\varepsilon \nabla c_i^\varepsilon\|_{L^2(\Omega_{i,\tau}^\varepsilon)}^2 &\leq \frac{1}{2} \|c_i^\varepsilon(0)\|_{L^2(\Omega_i^\varepsilon)}^2 + \langle F_i(c_i^\varepsilon), c_i^\varepsilon \rangle_{\Omega_{i,\tau}^\varepsilon} \\ &\quad + \varepsilon \langle G_i(p_a^\varepsilon, c_i^\varepsilon), c_i^\varepsilon \rangle_{\Gamma_\tau^\varepsilon}, \end{aligned}$$

for $\tau \in (0, T]$. Using the structure of G_e and G_i , the nonnegativity of solutions, and the assumptions on the coefficients in Assumption 3.1, together with the trace inequality (3.3) we obtain

$$(3.10) \quad \begin{aligned} \|c_e^\varepsilon(\tau)\|_{L^2(\Omega_\varepsilon)}^2 + \|\nabla c_e^\varepsilon\|_{L^2(\Omega_{\varepsilon,\tau}^\varepsilon)}^2 &\leq C \left[1 + \varepsilon \|r_b^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 + \|c_e^\varepsilon\|_{L^2(\Omega_{\varepsilon,\tau}^\varepsilon)}^2 \right], \\ \|c_i^\varepsilon(\tau)\|_{L^2(\Omega_i^\varepsilon)}^2 + \|\varepsilon \nabla c_i^\varepsilon\|_{L^2(\Omega_{i,\tau}^\varepsilon)}^2 &\leq C \left[1 + \varepsilon \|p_a^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 + \|c_i^\varepsilon\|_{L^2(\Omega_{i,\tau}^\varepsilon)}^2 \right]. \end{aligned}$$

Taking r_f^ε as a test function in the equation for r_f^ε , and using the nonnegativity of c_e^ε , r_f^ε and r_b^ε , the structure of G_e , and the assumptions on F_f we have

$$(3.11) \quad \varepsilon \|r_f^\varepsilon(\tau)\|_{L^2(\Gamma_\varepsilon)}^2 + \varepsilon \|\varepsilon \nabla_\Gamma r_f^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 \leq C \left[1 + \varepsilon \|r_b^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 + \varepsilon \|r_f^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 \right],$$

for $\tau \in (0, T]$. Considering the equation for the sum of r_b^ε and r_f^ε , taking $r_b^\varepsilon + r_f^\varepsilon$ as a test function, and using the structure of the function G_d , together with the nonnegativity of r_f^ε , r_b^ε , and p_d^ε and the estimate (3.11), yields

$$(3.12) \quad \begin{aligned} \varepsilon \|r_f^\varepsilon(\tau) + r_b^\varepsilon(\tau)\|_{L^2(\Gamma_\varepsilon)}^2 + \varepsilon \|\varepsilon \nabla_\Gamma r_b^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 &\leq C_1 \left[1 + \varepsilon \|\varepsilon \nabla_\Gamma r_f^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 \right. \\ &\quad \left. + \varepsilon \|r_f^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 + \varepsilon \|r_b^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 + \varepsilon \|p_a^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 \right] \\ &\leq C_2 \left[1 + \varepsilon \|r_b^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 + \varepsilon \|r_f^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 + \varepsilon \|p_a^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 \right], \end{aligned}$$

for $\tau \in (0, T]$. In a similar way as for r_f^ε , using the structure of G_d , the assumptions on F_d , and the nonnegativity of r_b^ε , p_d^ε and p_a^ε , we obtain

$$(3.13) \quad \varepsilon \|p_d^\varepsilon(\tau)\|_{L^2(\Gamma_\varepsilon)}^2 + \varepsilon \|\varepsilon \nabla_\Gamma p_d^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 \leq C \left[1 + \varepsilon \|p_a^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 + \varepsilon \|p_d^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 \right],$$

for $\tau \in (0, T]$. Considering the equation for the sum of p_d^ε and p_a^ε and taking $p_d^\varepsilon + p_a^\varepsilon$ as a test function yields

$$(3.14) \quad \begin{aligned} \varepsilon \|p_d^\varepsilon(\tau) + p_a^\varepsilon(\tau)\|_{L^2(\Gamma_\varepsilon)}^2 + \varepsilon \|\varepsilon \nabla_\Gamma p_a^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 &\leq C_1 \left[1 + \varepsilon \|\varepsilon \nabla_\Gamma p_d^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 \right. \\ &\quad \left. + \varepsilon \|p_a^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 + \varepsilon \|p_d^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 + \varepsilon \|c_i^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 \right] \\ &\leq C_2 \left[1 + \varepsilon \|p_a^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 + \varepsilon \|p_d^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 + \varepsilon \|c_i^\varepsilon\|_{L^2(\Gamma_\tau^\varepsilon)}^2 \right], \end{aligned}$$

for $\tau \in (0, T]$. Combining estimates (3.10)–(3.14) and using the Gronwall inequality and trace inequality (3.3), imply the a priori estimates stated in (3.5). \square

The main technical result of this section is the following uniform boundedness result. A number of the more laborious calculations are given in the Appendix C in order to aid readability of the manuscript.

LEMMA 3.9. *Under Assumptions 3.1 nonnegative solutions of problem (2.1)–(2.5) are bounded, uniformly in ε .*

Proof. To show boundedness of solutions to the microscopic model (2.1)–(2.5) we introduce the periodic unfolding operator $\mathcal{T}_{Y_l}^\varepsilon : L^p(\Omega_{l,T}^\varepsilon) \rightarrow L^p(\Omega_T \times Y_l)$, with $l = i, e$, and the boundary unfolding operator $\mathcal{T}_\Gamma^\varepsilon : L^p(\Gamma_T^\varepsilon) \rightarrow L^p(\Omega_T \times \Gamma)$, where $1 \leq p \leq \infty$, see Appendix B or e.g. [10, 11] for the definition and properties of the periodic unfolding operator. For simplification of the presentation we use the same notation \mathcal{T}^ε for the unfolding operator $\mathcal{T}_{Y_l}^\varepsilon$, for $l = e, i$, and the boundary unfolding operator $\mathcal{T}_\Gamma^\varepsilon$ as it is clear from the context which operator is applied.

Integration by parts in time of the terms in equations (3.1) and (3.2) that involve time derivatives, applying the unfolding operator and using the nonnegativity of the solutions, we obtain the following estimates for $x \in \Omega$, (to aid readability of the manuscript the details of the derivation of the estimates are given in Appendix C)

$$\begin{aligned}
 (3.15) \quad & \|\mathcal{T}^\varepsilon(r_f^\varepsilon)(\tau)\|_{L^2(\Gamma)}^2 + \|\nabla_{\Gamma,y}\mathcal{T}^\varepsilon(r_f^\varepsilon)\|_{L^2(\Gamma_\tau)}^2 + \|\mathcal{T}^\varepsilon(r_b^\varepsilon)(\tau)\|_{L^2(\Gamma)}^2 + \|\nabla_{\Gamma,y}\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^2(\Gamma_\tau)}^2 \\
 & \leq C \left[1 + \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^2(\Gamma_\tau)}^2 + \|\mathcal{T}^\varepsilon(r_f^\varepsilon)\|_{L^2(\Gamma_\tau)}^2 + \|\mathcal{T}^\varepsilon(p_a^\varepsilon)\|_{L^2(\Gamma_\tau)}^2 \right] \\
 & \|\mathcal{T}^\varepsilon(p_d^\varepsilon)(\tau)\|_{L^2(\Gamma)}^2 + \|\nabla_{\Gamma,y}\mathcal{T}^\varepsilon(p_d^\varepsilon)\|_{L^2(\Gamma_\tau)}^2 + \|\mathcal{T}^\varepsilon(p_a^\varepsilon)(\tau)\|_{L^2(\Gamma)}^2 + \|\nabla_{\Gamma,y}\mathcal{T}^\varepsilon(p_a^\varepsilon)\|_{L^2(\Gamma_\tau)}^2 \\
 & \leq C_1 \left[1 + \|\mathcal{T}^\varepsilon(p_a^\varepsilon)\|_{L^2(\Gamma_\tau)}^2 + \|\mathcal{T}^\varepsilon(p_d^\varepsilon)\|_{L^2(\Gamma_\tau)}^2 + \|\mathcal{T}^\varepsilon(c_i^\varepsilon)\|_{L^2(\Gamma_\tau)}^2 \right], \\
 & \|\mathcal{T}^\varepsilon(c_i^\varepsilon)(\tau)\|_{L^2(Y_i)}^2 + \|\nabla_y\mathcal{T}^\varepsilon(c_i^\varepsilon)\|_{L^2(Y_{i,\tau})}^2 \\
 & \leq C_3 \left[1 + \|\mathcal{T}^\varepsilon(c_i^\varepsilon)\|_{L^2(\Gamma_\tau)}^2 \right] + C_4 \left[\|\mathcal{T}^\varepsilon(c_i^\varepsilon)\|_{L^2(Y_{i,\tau})}^2 + \|\mathcal{T}^\varepsilon(p_a^\varepsilon)\|_{L^2(\Gamma_\tau)}^2 \right].
 \end{aligned}$$

Gronwall's inequality and a trace estimate for c_i^ε , similar to (3.3), yields for $x \in \Omega$,

$$\begin{aligned}
 (3.16) \quad & \|\mathcal{T}^\varepsilon(r_l^\varepsilon)\|_{L^\infty(0,T;L^2(\Gamma))} + \|\nabla_{\Gamma,y}\mathcal{T}^\varepsilon(r_l^\varepsilon)\|_{L^2(\Gamma_T)} \leq C, \quad \text{for } l = f, b, \\
 & \|\mathcal{T}^\varepsilon(p_s^\varepsilon)\|_{L^\infty(0,T;L^2(\Gamma))} + \|\nabla_{\Gamma,y}\mathcal{T}^\varepsilon(p_s^\varepsilon)\|_{L^2(\Gamma_T)} \leq C, \quad \text{for } s = d, a, \\
 & \|\mathcal{T}^\varepsilon(c_i^\varepsilon)\|_{L^\infty(0,T;L^2(Y_i))} + \|\nabla_y\mathcal{T}^\varepsilon(c_i^\varepsilon)\|_{L^2(Y_{i,T})} \leq C.
 \end{aligned}$$

Applying the Gagliardo-Nirenberg and trace inequalities and using the fact that $\dim(\Gamma) \leq 2$ we obtain for $l = f, b$ and $s = d, a$, and for $x \in \Omega$ and $\tau \in (0, T]$,

$$\begin{aligned}
 (3.17) \quad & \|\mathcal{T}^\varepsilon(r_l^\varepsilon)\|_{L^4(\Gamma_\tau)} \leq C_1 \|\nabla_{\Gamma,y}\mathcal{T}^\varepsilon(r_l^\varepsilon)\|_{L^2(\Gamma_\tau)}^{1/2} \|\mathcal{T}^\varepsilon(r_l^\varepsilon)\|_{L^\infty(0,\tau;L^2(\Gamma))}^{1/2} \leq C, \\
 & \|\mathcal{T}^\varepsilon(p_s^\varepsilon)\|_{L^4(\Gamma_\tau)} \leq C_2 \|\nabla_{\Gamma,y}\mathcal{T}^\varepsilon(p_s^\varepsilon)\|_{L^2(\Gamma_\tau)}^{1/2} \|\mathcal{T}^\varepsilon(p_s^\varepsilon)\|_{L^\infty(0,\tau;L^2(\Gamma))}^{1/2} \leq C, \\
 & \|\mathcal{T}^\varepsilon(c_i^\varepsilon)\|_{L^2(\Gamma_\tau)} \leq C_3 \left[\|\nabla_y\mathcal{T}^\varepsilon(c_i^\varepsilon)\|_{L^2(Y_{i,\tau})} + \|\mathcal{T}^\varepsilon(c_i^\varepsilon)\|_{L^2(Y_{i,\tau})} \right] \leq C, \\
 & \|\mathcal{T}^\varepsilon(c_i^\varepsilon)\|_{L^2(0,T;L^4(\Gamma))} \leq C_4 \left[\|\nabla_y\mathcal{T}^\varepsilon(c_i^\varepsilon)\|_{L^2(Y_{i,\tau})} + \|\mathcal{T}^\varepsilon(c_i^\varepsilon)\|_{L^2(Y_{i,\tau})} \right] \leq C,
 \end{aligned}$$

where the constant C is independent of ε and x . We also make use of the inequality

$$\begin{aligned}
 (3.18) \quad & \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^2(\Gamma)} \leq \mu \|\nabla_{\Gamma,y}\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^2(\Gamma)}^{1/2} \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^1(\Gamma)}^{1/2}, \\
 & \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^4(\Gamma)} \leq \mu \|\nabla_{\Gamma,y}\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^2(\Gamma)}^{1/2} \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^2(\Gamma)}^{1/2},
 \end{aligned}$$

for $x \in \Omega$, $t \in (0, T]$, and a constant $\mu > 0$ independent of ε .

The a priori estimates (3.5) and the properties of the unfolding operator, see Appendix B or [10] for more details, imply

$$(3.19) \quad \begin{aligned} \|\nabla_y \mathcal{T}^\varepsilon(c_e^\varepsilon)\|_{L^2(\Omega_T \times Y_e)} &= \|\varepsilon \mathcal{T}^\varepsilon(\nabla c_e^\varepsilon)\|_{L^2(\Omega_T \times Y_e)} \leq C_1 \|\varepsilon \nabla c_e^\varepsilon\|_{L^2(\Omega_{e,T}^\varepsilon)} \leq C_2 \varepsilon, \\ \|\nabla_y \mathcal{T}^\varepsilon(c_i^\varepsilon)\|_{L^2(\Omega_T \times Y_i)} &= \|\varepsilon \mathcal{T}^\varepsilon(\nabla c_i^\varepsilon)\|_{L^2(\Omega_T \times Y_i)} \leq C_3 \|\varepsilon \nabla c_i^\varepsilon\|_{L^2(\Omega_{i,T}^\varepsilon)} \leq C_4. \end{aligned}$$

Then using the Sobolev embedding theorem, where $\dim(Y_l) \leq 3$ for $l = e, i$, and the trace inequality we obtain

$$(3.20) \quad \begin{aligned} \|\mathcal{T}^\varepsilon(c_l^\varepsilon)\|_{L^2(\Omega_T \times \Gamma)} + \|\mathcal{T}^\varepsilon(c_l^\varepsilon)\|_{L^2(\Omega_T; L^4(\Gamma))} + \|\mathcal{T}^\varepsilon(c_l^\varepsilon)\|_{L^2(\Omega_T; L^4(Y_l))} \\ \leq \mu [\|\mathcal{T}^\varepsilon(c_l^\varepsilon)\|_{L^2(\Omega_T \times Y_l)} + \|\nabla_y \mathcal{T}^\varepsilon(c_l^\varepsilon)\|_{L^2(\Omega_T \times Y_l)}] \leq C, \end{aligned}$$

for $l = e, i$, where the constants $\mu > 0$ and $C > 0$ are independent of ε .

We now use an Alikakos iteration method [3] to prove the boundedness of solutions to (2.1)–(2.5). Considering first $|\mathcal{T}^\varepsilon(r_f^\varepsilon)|^{p-1}$, for $p \geq 4$, as a test function in the equation for $\mathcal{T}^\varepsilon(r_f^\varepsilon)$, (see (C.2) in Appendix C), using the assumptions on the function F_f , the nonnegativity of r_f^ε , r_b^ε and c_e^ε , and the Gagliardo-Nirenberg inequality we obtain the following estimate for $x \in \Omega$ and $\tau \in (0, T]$, (see Appendix C for the details)

$$(3.21) \quad \begin{aligned} \|\mathcal{T}^\varepsilon(r_f^\varepsilon)(\tau)\|_{L^p(\Gamma)}^p + \|\nabla_{\Gamma, y} |\mathcal{T}^\varepsilon(r_f^\varepsilon)|^{\frac{p}{2}}\|_{L^2(\Gamma_\tau)}^2 \\ \leq C_1 \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^4(\Gamma_\tau)}^p + C_2 p^4 \left(\sup_{(0, \tau)} \|\mathcal{T}^\varepsilon(r_f^\varepsilon)\|_{L^1(\Gamma)}^{\frac{p}{2}} + 1 \right). \end{aligned}$$

Then, the Alikakos iteration Lemma [3] ensures that for $x \in \Omega$

$$(3.22) \quad \|\mathcal{T}^\varepsilon(r_f^\varepsilon)\|_{L^\infty(0, T; L^\infty(\Gamma))} \leq C_1 [1 + \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^4(\Gamma_T)}] \leq C_2.$$

The definition of the unfolding operator and the fact that C_2 is independent of $x \in \Omega$ yields the boundedness of r_f^ε in $(0, T) \times \Gamma^\varepsilon$. Due to the structure of the reaction terms, in the same way as for $\mathcal{T}^\varepsilon(r_f^\varepsilon)$ we obtain

$$(3.23) \quad \|\mathcal{T}^\varepsilon(p_d^\varepsilon)\|_{L^\infty(0, T; L^\infty(\Gamma))} \leq C_1 [1 + \|\mathcal{T}^\varepsilon(p_a^\varepsilon)\|_{L^4(\Gamma_T)}] \leq C_2,$$

for $x \in \Omega$. To show the boundedness of c_e^ε we consider $|c_e^\varepsilon|^{p-1}$, for $p \geq 4$, as a test function in the first equation of (3.1) and, using the assumptions on F_e and the nonnegativity of r_f^ε and c_e^ε we obtain

$$(3.24) \quad \begin{aligned} \|c_e^\varepsilon(\tau)\|_{L^p(\Omega_e^\varepsilon)}^p + 4 \frac{p-1}{p} \|\nabla |c_e^\varepsilon|^{\frac{p}{2}}\|_{L^2(\Omega_{e,\tau}^\varepsilon)}^2 \leq C_1 p [1 + \|c_e^\varepsilon\|_{L^p(\Omega_{e,\tau}^\varepsilon)}^p] \\ + C_\delta p^3 \|c_e^\varepsilon\|_{L^p(\Omega_{e,\tau}^\varepsilon)}^p + \delta \frac{p-1}{p} \|\nabla |c_e^\varepsilon|^{\frac{p}{2}}\|_{L^2(\Omega_{e,\tau}^\varepsilon)}^2 + \int_{\Omega_\tau} \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^4(\Gamma)}^p dx dt. \end{aligned}$$

Using the boundedness of $\mathcal{T}^\varepsilon(r_f^\varepsilon)$ and taking $|\mathcal{T}^\varepsilon(r_b^\varepsilon)|^3$ as a test function in the equation for $\mathcal{T}^\varepsilon(r_b^\varepsilon)$ (see (C.2) in Appendix C) yields

$$(3.25) \quad \|\mathcal{T}^\varepsilon(r_b^\varepsilon)(\tau)\|_{L^4(\Gamma)} + \|\nabla_{\Gamma, y} |\mathcal{T}^\varepsilon(r_b^\varepsilon)|^2\|_{L^2(\Gamma_\tau)}^{\frac{1}{2}} \leq C [1 + \|\mathcal{T}^\varepsilon(c_e^\varepsilon)\|_{L^p(\Gamma_\tau)}],$$

for $\tau \in (0, T]$ and $x \in \Omega$. Combining the estimates (3.24) and (3.25) with a trace inequality and a Gagliardo-Nirenberg inequality, applied to the extension of c_e^ε from Ω_e^ε into Ω , (see Appendix C for more details) yields

$$(3.26) \quad \|c_e^\varepsilon(\tau)\|_{L^2(\Omega_e^\varepsilon)}^{\frac{p}{2}} + \|\nabla |c_e^\varepsilon|^{\frac{p}{2}}\|_{L^2(\Omega_{e,\tau}^\varepsilon)}^2 \leq C_\delta p^8 \left[\sup_{(0, \tau)} \|c_e^\varepsilon\|_{L^1(\Omega_e^\varepsilon)}^{\frac{p}{2}} + 1 \right].$$

Then the iteration over p , similar to [3], yields the boundedness of c_e^ε in $\Omega_{e,T}^\varepsilon$. Since $c_e^\varepsilon \in L^2(0, T; H^1(\Omega_e^\varepsilon))$ we also have the boundedness of c_e^ε on $(0, T) \times \Gamma^\varepsilon$, see e.g. [16].

To show boundedness of r_b^ε we consider $|\mathcal{T}^\varepsilon(r_b^\varepsilon)|^{p-1}$ as a test function in the equation for $\mathcal{T}^\varepsilon(r_b^\varepsilon)$ (equation (C.2) in Appendix C) and using the boundedness of $\mathcal{T}^\varepsilon(r_f^\varepsilon)$ we obtain

$$\begin{aligned} \|\mathcal{T}^\varepsilon(r_b^\varepsilon(\tau))\|_{L^p(\Gamma)}^p + 4\frac{p-1}{p}\|\nabla|\mathcal{T}^\varepsilon(r_b^\varepsilon)|^{\frac{p}{2}}\|_{L^2(\Gamma_\tau)}^2 &\leq C_1 p^4 [1 + \sup_{(0,\tau)} \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^1(\Gamma)}^{\frac{p}{2}}] \\ &\quad + C_2 [\|\mathcal{T}^\varepsilon(c_e^\varepsilon)\|_{L^4(\Gamma_\tau)}^p + \|\mathcal{T}^\varepsilon(p_a^\varepsilon)\|_{L^4(\Gamma_\tau)}^p], \end{aligned}$$

for $x \in \Omega$ and $\tau \in (0, T]$. The iteration over p , boundedness of c_e^ε , and estimate (3.17) for $\mathcal{T}^\varepsilon(p_a^\varepsilon)$ ensure boundedness of $\mathcal{T}^\varepsilon(r_b^\varepsilon)$ in $\Omega_T \times \Gamma$ and hence the boundedness of r_b^ε in $(0, T) \times \Gamma^\varepsilon$.

Taking $|\mathcal{T}^\varepsilon(p_a^\varepsilon)|^{p-1}$ as a test function in the equation for $\mathcal{T}^\varepsilon(p_a^\varepsilon)$, (equation (C.2) in Appendix C) and using the boundedness of $\mathcal{T}^\varepsilon(p_a^\varepsilon)$ yield

$$\begin{aligned} \|\mathcal{T}^\varepsilon(p_a^\varepsilon(\tau))\|_{L^p(\Gamma)}^p + 4\frac{p-1}{p}\|\nabla|\mathcal{T}^\varepsilon(p_a^\varepsilon)|^{\frac{p}{2}}\|_{L^2(\Gamma_\tau)}^2 &\leq C_1 p^4 [1 + \sup_{(0,\tau)} \|\mathcal{T}^\varepsilon(p_a^\varepsilon)\|_{L^1(\Gamma)}^{\frac{p}{2}}] \\ &\quad + C_2 \sup_{(0,\tau)} \|\mathcal{T}^\varepsilon(c_i^\varepsilon)\|_{L^1(Y_i)}^{\frac{p}{2}} + \delta \|\nabla_{\Gamma,y}|\mathcal{T}^\varepsilon(c_i^\varepsilon)|^{\frac{p}{2}}\|_{L^2(Y_{i,\tau})}^2 + C_3 \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^4(\Gamma_\tau)}^p, \end{aligned}$$

for $x \in \Omega$ and $\tau \in (0, T]$. Similarly considering $|\mathcal{T}^\varepsilon(c_i^\varepsilon)|^{p-1}$ as a test function in the equation for $\mathcal{T}^\varepsilon(c_i^\varepsilon)$, (see (C.1) in Appendix C), gives

$$\begin{aligned} \|\mathcal{T}^\varepsilon(c_i^\varepsilon(\tau))\|_{L^p(Y_i)}^p + 4\frac{p-1}{p}\|\nabla|\mathcal{T}^\varepsilon(c_i^\varepsilon)|^{\frac{p}{2}}\|_{L^2(Y_{i,\tau})}^2 &\leq C_\delta p^4 [1 + \sup_{(0,\tau)} \|\mathcal{T}^\varepsilon(c_i^\varepsilon)\|_{L^1(Y_i)}^{\frac{p}{2}}] \\ &\quad + \delta \|\nabla_{\Gamma,y}|\mathcal{T}^\varepsilon(c_i^\varepsilon)|^{\frac{p}{2}}\|_{L^2(Y_{i,\tau})}^2 + C_\delta \sup_{(0,\tau)} \|\mathcal{T}^\varepsilon(p_a^\varepsilon)\|_{L^1(\Gamma)}^{\frac{p}{2}} + \delta \|\nabla|\mathcal{T}^\varepsilon(p_a^\varepsilon)|^{\frac{p}{2}}\|_{L^2(\Gamma_\tau)}^2, \end{aligned}$$

for $x \in \Omega$ and $\tau \in (0, T]$. Adding the last two inequalities, using the boundedness of $\|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^4(\Gamma_\tau)} \leq C$, for $x \in \Omega$ and $\tau \in (0, T]$, and iterating over p we obtain the boundedness of $\mathcal{T}^\varepsilon(p_a^\varepsilon)$ in $\Omega_T \times \Gamma$ and of $\mathcal{T}^\varepsilon(c_i^\varepsilon)$ in $\Omega_T \times Y_i$. This also ensures the boundedness of p_a^ε in $(0, T) \times \Gamma^\varepsilon$ and of c_i^ε in $(0, T) \times \Omega_i^\varepsilon$ and $(0, T) \times \Gamma^\varepsilon$. \square

LEMMA 3.10. *The solution to the microscopic problem (2.1)–(2.5) is unique.*

Proof. Uniqueness follows from standard arguments by taking the difference of two solutions and using the boundedness of solutions, shown in Lemma 3.9, together with the local Lipschitz continuity of the nonlinear reaction terms. \square

4. Convergence results and derivation of macroscopic equations. In this section, we use the a priori estimates of Theorem 3.5 to deduce the convergence upto a subsequence of solutions of the microscopic problem (2.1)–(2.5) to solutions of a limiting two-scale problem. We make use of the theory of two-scale convergence to pass to the limit and the necessary definitions and results are stated in Appendix B

In the convergence results stated below we consider the H^1 -extension of c_e^ε from Ω_e^ε into Ω , which is well defined due to the assumptions on the geometry of Ω_e^ε , see e.g. Remark 3.4 or [2, 9] and we identify c_e^ε with this extension. By $[c_e^\varepsilon]^\sim$ we will denote the extension of c_e^ε by zero from Ω_e^ε into Ω and by χ_{Y_e} the characteristic function of Y_e . The space $H_{\text{per}}^1(Y)$ is defined as the closure of $C_{\text{per}}^1(Y)$ with respect to the H^1 -norm.

LEMMA 4.1. *There exist functions $c_e \in L^2(0, T; H^1(\Omega))$, $c_e^1 \in L^2(\Omega_T; H_{\text{per}}^1(Y))$, $c_i \in L^2(\Omega_T; H^1(Y_i))$ and $r_l, p_s \in L^2(\Omega_T; H^1(\Gamma))$, with $l = f, b$ and $s = a, d$, such that, up to a subsequence,*

$$\begin{aligned}
 (4.1) \quad & c_e^\varepsilon \rightharpoonup c_e && \text{weakly in } L^2(0, T; H^1(\Omega)), \\
 & \nabla c_e^\varepsilon \rightharpoonup \nabla c_e + \nabla_y c_e^1 && \text{two-scale,} \\
 & [c_e^\varepsilon]^\sim \rightharpoonup c_e \chi_{Y_e}, \quad [\nabla c_e^\varepsilon]^\sim \rightharpoonup (\nabla c_e + \nabla_y c_e^1) \chi_{Y_e} && \text{two-scale,} \\
 & c_i^\varepsilon \rightharpoonup c_i, \quad \varepsilon \nabla c_i^\varepsilon \rightharpoonup \nabla_y c_i && \text{two-scale,} \\
 & r_l^\varepsilon \rightharpoonup r_l, \quad \varepsilon \nabla_\Gamma r_l^\varepsilon \rightharpoonup \nabla_{\Gamma, y} r_l && \text{two-scale,} \quad l = f, b, \\
 & p_s^\varepsilon \rightharpoonup p_s, \quad \varepsilon \nabla_\Gamma p_s^\varepsilon \rightharpoonup \nabla_{\Gamma, y} p_s && \text{two-scale,} \quad s = a, d.
 \end{aligned}$$

Proof. The convergence results in (4.1) follow directly from the a priori estimates (3.5), the extension of c_e^ε from Ω_e^ε into Ω and compactness theorems for the weak convergence and for the two-scale convergence, see e.g. [4, 5, 43, 44] and Appendix B. Notice that since the extension of c_e^ε and $[c_e^\varepsilon]^\sim$ coincide in Ω_e^ε , we obtain the same function c_e in the two-scale limit for both sequences $\{c_e^\varepsilon\}$ and $\{[c_e^\varepsilon]^\sim\}$. \square

In order to pass to the limit in nonlinear reaction terms we prove strong convergence upto a subsequence of solutions of the microscopic problem (2.1)–(2.5).

LEMMA 4.2. *For a subsequence of a sequence of solutions of microscopic model (2.1)–(2.5), i.e. $\{c_e^\varepsilon\}$, $\{\mathcal{T}^\varepsilon(c_i^\varepsilon)\}$, $\{\mathcal{T}^\varepsilon(r_l^\varepsilon)\}$, and $\{\mathcal{T}^\varepsilon(p_s^\varepsilon)\}$, where $l = f, b$ and $s = a, d$, we have the following convergence results:*

$$\begin{aligned}
 (4.2) \quad & c_e^\varepsilon \rightarrow c_e \quad \text{strongly in } L^2(\Omega_T), \quad \varepsilon \|c_e^\varepsilon - c_e\|_{L^2(\Gamma_T^\varepsilon)}^2 \rightarrow 0, \\
 & \mathcal{T}^\varepsilon(c_e^\varepsilon) \rightarrow c_e \quad \text{strongly in } L^2(\Omega_T \times Y_e) \text{ and } L^2(\Omega_T \times \Gamma), \\
 & \mathcal{T}^\varepsilon(c_i^\varepsilon) \rightarrow c_i \quad \text{strongly in } L^2(\Omega_T \times Y_i), \\
 & \mathcal{T}^\varepsilon(r_l^\varepsilon) \rightarrow r_l \quad \text{strongly in } L^2(\Omega_T \times \Gamma), \quad l = f, b \\
 & \mathcal{T}^\varepsilon(p_s^\varepsilon) \rightarrow p_s \quad \text{strongly in } L^2(\Omega_T \times \Gamma), \quad s = a, d,
 \end{aligned}$$

as $\varepsilon \rightarrow 0$.

Proof. We first show the equicontinuity of c_e^ε with respect to the time variable. The a priori estimates in (3.5) and the boundedness of r_f^ε yield

$$\begin{aligned}
 \|\vartheta_\delta c_e^\varepsilon - c_e^\varepsilon\|_{L^2(\Omega_{e, \tau}^\varepsilon)}^2 &\leq C_1 \int_{\Omega_{e, \tau}^\varepsilon} \int_t^{t+\delta} |\nabla c_e^\varepsilon| ds |\nabla(\vartheta_\delta c_e^\varepsilon - c_e^\varepsilon)| dx dt \\
 &\quad + C_2 \int_{\Omega_{e, \tau}^\varepsilon} \int_t^{t+\delta} (1 + |c_e^\varepsilon|) ds |\vartheta_\delta c_e^\varepsilon - c_e^\varepsilon| dx dt \\
 &\quad + \varepsilon C_3 \int_{\Gamma_\tau^\varepsilon} \int_t^{t+\delta} (|c_e^\varepsilon r_f^\varepsilon| + |r_b^\varepsilon|) ds |\vartheta_\delta c_e^\varepsilon - c_e^\varepsilon| d\sigma^\varepsilon dt \leq C\delta,
 \end{aligned}$$

for $\tau \in (0, T - \delta]$ and $\delta > 0$, where $\vartheta_\delta v(t, x) = v(t + \delta, x)$ for $x \in \Omega$ and $t \in [0, T - \delta]$. Then the properties of an extension of c_e^ε from Ω_e^ε into Ω together with the uniform in ε estimate for ∇c_e^ε and a Kolmogorov compactness result [8] ensure the strong convergence of c_e^ε in $L^2((0, T) \times \Omega)$. Applying the Simon compactness theorem [47] and the compact embedding of $H^1(\Omega)$ into $H^\beta(\Omega)$ for $1/2 < \beta < 1$, together with the trace inequality and a scaling argument, similar to [37], we also obtain $\varepsilon \|c_e^\varepsilon - c_e\|_{L^2(\Gamma_T^\varepsilon)}^2 \rightarrow 0$

as $\varepsilon \rightarrow 0$.

The properties of the unfolding operator, see [10] and Appendix B, imply

$$\|\mathcal{T}^\varepsilon(c_e^\varepsilon)\|_{L^2(\Omega_T \times Y_e)} \leq |Y|^{\frac{1}{2}} \|c_e^\varepsilon\|_{L^2(\Omega_{e,T}^\varepsilon)}, \quad \|\mathcal{T}^\varepsilon(c_e^\varepsilon)\|_{L^2(\Omega_T \times \Gamma)} \leq |Y|^{\frac{1}{2}} \varepsilon^{\frac{1}{2}} \|c_e^\varepsilon\|_{L^2(\Gamma_T^\varepsilon)},$$

and for $c_e \in L^2(\Omega_T)$, considered as constant with respect to $y \in Y_e$ or $y \in \Gamma$, respectively, we have $\mathcal{T}^\varepsilon(c_e) \rightarrow c_e$ strongly in $L^2(\Omega_T \times Y_e)$ and in $L^2(\Omega_T \times \Gamma)$ as $\varepsilon \rightarrow 0$. Then we obtain

$$\begin{aligned} \|\mathcal{T}^\varepsilon(c_e^\varepsilon) - c_e\|_{L^2(\Omega_T \times Y_e)} &\leq \|\mathcal{T}^\varepsilon(c_e^\varepsilon) - \mathcal{T}^\varepsilon(c_e)\|_{L^2(\Omega_T \times Y_e)} + \|\mathcal{T}^\varepsilon(c_e) - c_e\|_{L^2(\Omega_T \times Y_e)} \\ &\leq |Y|^{\frac{1}{2}} \|c_e^\varepsilon - c_e\|_{L^2(\Omega_{e,T}^\varepsilon)} + \|\mathcal{T}^\varepsilon(c_e) - c_e\|_{L^2(\Omega_T \times Y_e)}, \\ \|\mathcal{T}^\varepsilon(c_e^\varepsilon) - c_e\|_{L^2(\Omega_T \times \Gamma)} &\leq \varepsilon^{\frac{1}{2}} |Y|^{\frac{1}{2}} \|c_e^\varepsilon - c_e\|_{L^2(\Gamma_T^\varepsilon)} + \|\mathcal{T}^\varepsilon(c_e) - c_e\|_{L^2(\Omega_T \times \Gamma)}. \end{aligned}$$

Hence the strong convergence of $\{c_e^\varepsilon\}$ in $L^2(\Omega_T)$ and the convergence result for $\varepsilon \|c_e^\varepsilon - c_e\|_{L^2(\Gamma_T^\varepsilon)}^2$ in (4.2) ensure the strong convergence of $\{\mathcal{T}^\varepsilon(c_e^\varepsilon)\}$ in $L^2(\Omega_T \times Y_e)$ and in $L^2(\Omega_T \times \Gamma)$, respectively.

To obtain the strong convergence of $\mathcal{T}^\varepsilon(c_i^\varepsilon)$, $\mathcal{T}^\varepsilon(r_l^\varepsilon)$, and $\mathcal{T}^\varepsilon(p_s^\varepsilon)$, with $l = f, b$ and $s = a, d$, we show the Cauchy property for the corresponding sequences. Considering the difference of equations for ε_m and ε_k and using the boundedness of c_e^ε , r_f^ε , and r_b^ε yields

$$\begin{aligned} &\sum_{l=f,b} \|\mathcal{T}^{\varepsilon_m}(r_l^{\varepsilon_m}(\tau)) - \mathcal{T}^{\varepsilon_k}(r_l^{\varepsilon_k}(\tau))\|_{L^2(\Omega \times \Gamma)}^2 + \|\nabla_{\Gamma,y}(\mathcal{T}^{\varepsilon_m}(r_l^{\varepsilon_m}) - \mathcal{T}^{\varepsilon_k}(r_l^{\varepsilon_k}))\|_{L^2(\Omega_\tau \times \Gamma)}^2 \\ &\leq C_1 \left[\|\mathcal{T}^{\varepsilon_m}(c_e^{\varepsilon_m}) - \mathcal{T}^{\varepsilon_k}(c_e^{\varepsilon_k})\|_{L^2(\Omega_\tau \times \Gamma)}^2 + \sum_{l=f,b} \|\mathcal{T}^{\varepsilon_m}(r_l^{\varepsilon_m}) - \mathcal{T}^{\varepsilon_k}(r_l^{\varepsilon_k})\|_{L^2(\Omega_\tau \times \Gamma)}^2 \right] \\ &+ C_2 \left[\sum_{j=a,d} \|\mathcal{T}^{\varepsilon_m}(p_j^{\varepsilon_m}) - \mathcal{T}^{\varepsilon_k}(p_j^{\varepsilon_k})\|_{L^2(\Omega_\tau \times \Gamma)}^2 + \sum_{l=f,b} \|\mathcal{T}^{\varepsilon_m}(r_{l,0}^{\varepsilon_m}) - \mathcal{T}^{\varepsilon_k}(r_{l,0}^{\varepsilon_k})\|_{L^2(\Omega \times \Gamma)}^2 \right], \end{aligned}$$

for $\tau \in (0, T]$. Similarly, the boundedness of p_d^ε yields

$$\begin{aligned} &\sum_{j=a,d} \|\mathcal{T}^{\varepsilon_m}(p_j^{\varepsilon_m}(\tau)) - \mathcal{T}^{\varepsilon_k}(p_j^{\varepsilon_k}(\tau))\|_{L^2(\Omega \times \Gamma)}^2 + \|\nabla_{\Gamma,y}(\mathcal{T}^{\varepsilon_m}(p_j^{\varepsilon_m}) - \mathcal{T}^{\varepsilon_k}(p_j^{\varepsilon_k}))\|_{L^2(\Omega_\tau \times \Gamma)}^2 \\ &\leq C_1 \sum_{j=a,d} \left[\|\mathcal{T}^{\varepsilon_m}(p_j^{\varepsilon_m}) - \mathcal{T}^{\varepsilon_k}(p_j^{\varepsilon_k})\|_{L^2(\Omega_\tau \times \Gamma)}^2 + \|\mathcal{T}^{\varepsilon_m}(p_{j,0}^{\varepsilon_m}) - \mathcal{T}^{\varepsilon_k}(p_{j,0}^{\varepsilon_k})\|_{L^2(\Omega \times \Gamma)}^2 \right] \\ &+ C_2 \left[\|\mathcal{T}^{\varepsilon_m}(r_b^{\varepsilon_m}) - \mathcal{T}^{\varepsilon_k}(r_b^{\varepsilon_k})\|_{L^2(\Omega_\tau \times \Gamma)}^2 + \|\mathcal{T}^{\varepsilon_m}(c_i^{\varepsilon_m}) - \mathcal{T}^{\varepsilon_k}(c_i^{\varepsilon_k})\|_{L^2(\Omega_\tau \times \Gamma)}^2 \right]. \end{aligned}$$

For $\mathcal{T}^\varepsilon(c_i^\varepsilon)$ the trace inequality implies

$$\begin{aligned} &\|\mathcal{T}^{\varepsilon_m}(c_i^{\varepsilon_m}(\tau)) - \mathcal{T}^{\varepsilon_k}(c_i^{\varepsilon_k}(\tau))\|_{L^2(\Omega \times Y_i)}^2 + \|\nabla_y(\mathcal{T}^{\varepsilon_m}(c_i^{\varepsilon_m}) - \mathcal{T}^{\varepsilon_k}(c_i^{\varepsilon_k}))\|_{L^2(\Omega_\tau \times Y_i)}^2 \\ &\leq C_\delta \|\mathcal{T}^{\varepsilon_m}(c_i^{\varepsilon_m}) - \mathcal{T}^{\varepsilon_k}(c_i^{\varepsilon_k})\|_{L^2(\Omega_\tau \times Y_i)}^2 + \delta \|\nabla_y(\mathcal{T}^{\varepsilon_m}(c_i^{\varepsilon_m}) - \mathcal{T}^{\varepsilon_k}(c_i^{\varepsilon_k}))\|_{L^2(\Omega_\tau \times Y_i)}^2 \\ &+ C_1 \left[\|\mathcal{T}^{\varepsilon_m}(p_a^{\varepsilon_m}) - \mathcal{T}^{\varepsilon_k}(p_a^{\varepsilon_k})\|_{L^2(\Omega_\tau \times \Gamma)}^2 + \|\mathcal{T}^{\varepsilon_m}(c_{i,0}^{\varepsilon_m}) - \mathcal{T}^{\varepsilon_k}(c_{i,0}^{\varepsilon_k})\|_{L^2(\Omega \times Y_i)}^2 \right]. \end{aligned}$$

Using the three estimates above, the strong convergence of the initial conditions and the strong convergence of $\{\mathcal{T}^\varepsilon(c_e^\varepsilon)\}$ in $L^2(\Omega_T \times \Gamma)$ we obtain the Cauchy property and hence the strong convergence upto subsequences of $\{\mathcal{T}^\varepsilon(c_i^\varepsilon)\}$, $\{\mathcal{T}^\varepsilon(r_l^\varepsilon)\}$, and $\{\mathcal{T}^\varepsilon(p_s^\varepsilon)\}$, with $l = f, b$ and $s = a, d$. \square

The convergence results in Lemmata 4.1 and 4.2 allow us to derive the corresponding macroscopic equations obtained in the limit as $\varepsilon \rightarrow 0$ from the microscopic model (2.1)–(2.5).

THEOREM 4.3. *A sequence $\{c_e^\varepsilon, c_i^\varepsilon, r_f^\varepsilon, r_b^\varepsilon, p_a^\varepsilon, p_d^\varepsilon\}$ of solutions of (2.1)–(2.5) converge as $\varepsilon \rightarrow 0$ to functions $c_e \in L^2(0, T; H^1(\Omega))$, $c_i \in L^2(0, T; L^2(\Omega; H^1(Y_i)))$ and $r_l, p_s \in L^2(0, T; L^2(\Omega; H^1(\Gamma)))$, for $l = f, b$, $s = a, d$, that satisfy the following macroscopic equations:*

$$(4.3) \quad \begin{aligned} \theta_e \partial_t c_e - \nabla \cdot (D_e^{\text{hom}}(x) \nabla c_e) &= \theta_e F_e(c_e) - \frac{1}{|Y|} \int_{\Gamma} G_e(c_e, r_f, r_b) d\sigma_y && \text{in } \Omega, \\ D_e^{\text{hom}}(x) \nabla c_e \cdot \nu &= 0 && \text{on } \partial\Omega, \\ \partial_t c_i - \nabla_y \cdot (D_i(y) \nabla_y c_i) &= F_i(c_i) && \text{in } \Omega \times Y_i, \\ D_i(y) \nabla_y c_i \cdot \nu &= G_i(p_a, c_i) && \text{on } \Omega \times \Gamma, \end{aligned}$$

where $\theta_e = |Y_e|/|Y|$, and

$$D_{e,ij}^{\text{hom}}(x) = \frac{1}{|Y|} \int_{Y_e} [D_{e,ij}(x, y) + (D_e(x, y) \nabla_y w^j(y))_i] dy,$$

with w^j being solutions of the unit cell problems

$$\begin{aligned} \operatorname{div}_y (D_e(x, y) (\nabla_y w^j + e_j)) &= 0 && \text{in } Y_e \times \Omega, \quad \int_{Y_e} w^j(x, y) dy = 0, \\ D_e(x, y) (\nabla_y w^j + e_j) \cdot \nu &= 0 && \text{on } \Gamma \times \Omega, \quad w^j(x, \cdot) \text{ } Y\text{-periodic}, \end{aligned}$$

for $x \in \Omega$, where $\{e_j\}_{j=1,\dots,d}$ is the standard basis in \mathbb{R}^d , together with the dynamics of receptors and proteins on the cell membrane $\Omega \times \Gamma$

$$(4.4) \quad \begin{aligned} \partial_t r_f - \nabla_{\Gamma,y} \cdot (D_f \nabla_{\Gamma,y} r_f) &= F_f(r_f, r_b) - G_e(c_e, r_f, r_b) - d_f r_f, \\ \partial_t r_b - \nabla_{\Gamma,y} \cdot (D_b \nabla_{\Gamma,y} r_b) &= G_e(c_e, r_f, r_b) - G_d(r_b, p_d, p_a) - d_b r_b, \\ \partial_t p_d - \nabla_{\Gamma,y} \cdot (D_d \nabla_{\Gamma,y} p_d) &= F_d(p_d) - G_d(r_b, p_d, p_a) - d_d p_d, \\ \partial_t p_a - \nabla_{\Gamma,y} \cdot (D_a \nabla_{\Gamma,y} p_a) &= G_d(r_b, p_d, p_a) - G_i(p_a, c_i) - d_a p_a, \end{aligned}$$

and initial conditions

$$(4.5) \quad \begin{aligned} c_e(0, x) &= c_{e,0}(x) \text{ for } x \in \Omega, \quad c_i(0, x, y) = c_{i,1}(x) c_{i,2}(y) \text{ for } x \in \Omega, y \in Y_i, \\ r_j(0, x, y) &= r_{j,1}(x) r_{j,2}(y), \quad p_s(0, x, y) = p_{s,1}(x) p_{s,2}(y) \text{ for } x \in \Omega, y \in \Gamma, \end{aligned}$$

where $j = f, b$ and $s = a, d$.

Proof. To derive the macroscopic problem take $\phi^\varepsilon(t, x) = \phi_1(t, x) + \varepsilon \phi_2(t, x, x/\varepsilon)$, where $\phi_1 \in H^1(\Omega_T)$ and $\phi_2 \in C_0^1(\Omega_T; C_{\text{per}}(Y))$, and $\psi^\varepsilon(t, x) = \psi_1(t, x, x/\varepsilon)$, with $\psi_1 \in C^1([0, T]; C_0^1(\Omega; H^1(Y_i)))$, as test functions in (3.1) and $\varphi^\varepsilon(t, x) = \varphi_1(t, x, x/\varepsilon)$, with $\varphi_1 \in C^1([0, T]; C_0^1(\Omega; H^1(\Gamma)))$, as a test function in (3.2), respectively, where ψ_1 and φ_1 are Y -periodically extended to \mathbb{R}^d . Then we obtain

$$(4.6) \quad \begin{aligned} \langle \partial_t c_e^\varepsilon, \phi_1 + \varepsilon \phi_2 \rangle + \langle D_e^\varepsilon(x) \nabla c_e^\varepsilon, \nabla(\phi_1 + \varepsilon \phi_2) + \nabla_y \phi_2 \rangle_{\Omega_{e,T}^\varepsilon} &= \langle F_e(c_e^\varepsilon), \phi_1 + \varepsilon \phi_2 \rangle_{\Omega_{e,T}^\varepsilon} \\ &\quad - \varepsilon \langle G_e(c_e^\varepsilon, r_f^\varepsilon, r_b^\varepsilon), \phi_1 + \varepsilon \phi_2 \rangle_{\Gamma_T^\varepsilon}, \\ \langle \partial_t c_i^\varepsilon, \psi_1 \rangle + \langle \varepsilon D_i^\varepsilon(x) \nabla c_i^\varepsilon, \varepsilon \nabla \psi_1 + \nabla_y \psi_1 \rangle_{\Omega_{i,T}^\varepsilon} &= \langle F_i(c_i^\varepsilon), \psi_1 \rangle_{\Omega_{i,T}^\varepsilon} + \varepsilon \langle G_i(p_a^\varepsilon, c_i^\varepsilon), \psi_1 \rangle_{\Gamma_T^\varepsilon}, \end{aligned}$$

and

$$\begin{aligned}
(4.7) \quad & \varepsilon \langle \partial_t r_f^\varepsilon, \varphi_1 \rangle + \varepsilon \langle \varepsilon D_f \nabla_\Gamma r_f^\varepsilon, \varepsilon \nabla_\Gamma \varphi_1 + \nabla_{\Gamma, y} \varphi_1 \rangle_{\Gamma_T^\varepsilon} \\
& = \varepsilon \langle F_f(r_f^\varepsilon, r_b^\varepsilon) - G_e(c_e^\varepsilon, r_f^\varepsilon, r_b^\varepsilon) - d_f r_f^\varepsilon, \varphi_1 \rangle_{\Gamma_T^\varepsilon}, \\
& \varepsilon \langle \partial_t r_b^\varepsilon, \varphi_1 \rangle + \varepsilon \langle \varepsilon D_b \nabla_\Gamma r_b^\varepsilon, \varepsilon \nabla_\Gamma \varphi_1 + \nabla_{\Gamma, y} \varphi_1 \rangle_{\Gamma_T^\varepsilon} \\
& = \varepsilon \langle G_e(c_e^\varepsilon, r_f^\varepsilon, r_b^\varepsilon) - G_d(r_b^\varepsilon, p_d^\varepsilon, p_a^\varepsilon) - d_b r_b^\varepsilon, \varphi_1 \rangle_{\Gamma_T^\varepsilon}, \\
& \varepsilon \langle \partial_t p_d^\varepsilon, \varphi_1 \rangle + \varepsilon \langle \varepsilon D_d \nabla_\Gamma p_d^\varepsilon, \varepsilon \nabla_\Gamma \varphi_1 + \nabla_{\Gamma, y} \varphi_1 \rangle_{\Gamma_T^\varepsilon} \\
& = \varepsilon \langle F_d(p_d^\varepsilon) - G_d(r_b^\varepsilon, p_d^\varepsilon, p_a^\varepsilon) - d_d p_d^\varepsilon, \varphi_1 \rangle_{\Gamma_T^\varepsilon}, \\
& \varepsilon \langle \partial_t p_a^\varepsilon, \varphi_1 \rangle + \varepsilon \langle \varepsilon D_a \nabla_\Gamma p_a^\varepsilon, \varepsilon \nabla_\Gamma \varphi_1 + \nabla_{\Gamma, y} \varphi_1 \rangle_{\Gamma_T^\varepsilon} \\
& = \varepsilon \langle G_d(r_b^\varepsilon, p_d^\varepsilon, p_a^\varepsilon) - G_i(p_a^\varepsilon, c_i^\varepsilon) - d_a p_a^\varepsilon, \varphi_1 \rangle_{\Gamma_T^\varepsilon}.
\end{aligned}$$

Considering first $\phi_1 \in H^1(\Omega_T)$ with $\phi_1(0, x) = 0$ and $\phi_1(T, x) = 0$ for $x \in \Omega$ and using integration by parts and the two-scale converge results, see Lemma 4.1, yield

$$\lim_{\varepsilon \rightarrow 0} \langle \partial_t c_e^\varepsilon, \phi_1 + \varepsilon \phi_2 \rangle = - \lim_{\varepsilon \rightarrow 0} \langle c_e^\varepsilon, \partial_t \phi_1 + \varepsilon \partial_t \phi_2 \rangle_{\Omega_{e, T}^\varepsilon} = -|Y|^{-1} \langle c_e, \partial_t \phi_1 \rangle_{Y_e \times \Omega_T}.$$

Similar calculations ensure convergence of $\langle \partial_t c_i^\varepsilon, \psi_1 \rangle$, $\varepsilon \langle \partial_t r_l^\varepsilon, \varphi_1 \rangle$, and $\varepsilon \langle \partial_t p_s^\varepsilon, \varphi_1 \rangle$, with $l = f, b$ and $s = a, d$. The two-scale convergence results, see Lemma 4.1, directly imply

$$\begin{aligned}
& \lim_{\varepsilon \rightarrow 0} \langle D_e^\varepsilon(x) \nabla c_e^\varepsilon, \nabla(\phi_1 + \varepsilon \phi_2) + \nabla_y \phi_2 \rangle_{\Omega_{e, T}^\varepsilon} \\
& = \frac{1}{|Y|} \langle D_e(x, y) (\nabla c_e + \nabla_y c_e^1), \nabla \phi_1 + \nabla_y \phi_2 \rangle_{Y_e \times \Omega_T} \\
& \lim_{\varepsilon \rightarrow 0} \langle \varepsilon D_i^\varepsilon(x) \nabla c_i^\varepsilon, \varepsilon \nabla \psi_1 + \nabla_y \psi_1 \rangle_{\Omega_{i, T}^\varepsilon} = \frac{1}{|Y|} \langle D_i(y) \nabla_y c_i, \nabla_y \psi_1 \rangle_{Y_i \times \Omega_T}, \\
& \lim_{\varepsilon \rightarrow 0} \varepsilon \langle \varepsilon D_f \nabla_\Gamma r_f^\varepsilon, \varepsilon \nabla_\Gamma \varphi_1 + \nabla_{\Gamma, y} \varphi_1 \rangle_{\Gamma_T^\varepsilon} = \frac{1}{|Y|} \langle D_f \nabla_{\Gamma, y} r_f, \nabla_{\Gamma, y} \varphi_1 \rangle_{\Gamma \times \Omega_T},
\end{aligned}$$

and convergence of the linear term $\varepsilon \langle d_f r_f^\varepsilon, \varphi_1 \rangle_{\Gamma_T^\varepsilon} \rightarrow |Y|^{-1} \langle d_f r_f, \varphi_1 \rangle_{\Gamma \times \Omega_T}$ as $\varepsilon \rightarrow 0$. The convergence of the corresponding terms in equations for r_b^ε , p_a^ε , and p_d^ε is obtained in the same way.

To pass to the limit in the nonlinear reaction terms we use the strong convergence results proven in Lemma 4.2. The definition and properties of the unfolding operator (c.f., Appendix B), together with the assumptions on functions F_l and G_j , for $l = e, i, f, d$ and $j = e, d, i$ and the boundedness of solutions of the microscopic problem (2.1)–(2.5), imply

$$\begin{aligned}
& \|F_l(\mathcal{T}^\varepsilon(c_l^\varepsilon))\|_{L^2(\Omega_T \times Y_l)} \leq |Y|^{\frac{1}{2}} \|F_l(c_l^\varepsilon)\|_{L^2(\Omega_{l, T}^\varepsilon)} \leq C_1(1 + \|c_l^\varepsilon\|_{L^2(\Omega_{l, T}^\varepsilon)}) \leq C_2, \\
& \|G_e(\mathcal{T}^\varepsilon(c_e^\varepsilon), \mathcal{T}^\varepsilon(r_f^\varepsilon), \mathcal{T}^\varepsilon(r_b^\varepsilon))\|_{L^2(\Omega_T \times \Gamma)} \leq \varepsilon^{\frac{1}{2}} |Y|^{\frac{1}{2}} \|G_e(c_e^\varepsilon, r_f^\varepsilon, r_b^\varepsilon)\|_{L^2(\Gamma_T^\varepsilon)} \leq C.
\end{aligned}$$

Here we used the fact that $\mathcal{T}^\varepsilon(F_l(c_l^\varepsilon)) = F_l(\mathcal{T}^\varepsilon(c_l^\varepsilon))$, for $l = e, i$, $\mathcal{T}^\varepsilon(G_e(c_e^\varepsilon, r_f^\varepsilon, r_b^\varepsilon)) = G_e(\mathcal{T}^\varepsilon(c_e^\varepsilon), \mathcal{T}^\varepsilon(r_f^\varepsilon), \mathcal{T}^\varepsilon(r_b^\varepsilon))$.

Similar estimates hold for F_f , F_d , G_d and G_i . Then the strong convergence of $\{\mathcal{T}^\varepsilon(c_l^\varepsilon)\}$, $\{\mathcal{T}^\varepsilon(r_j^\varepsilon)\}$, and $\{\mathcal{T}^\varepsilon(p_s^\varepsilon)\}$, with $l = e, i$, $s = a, d$, and $j = f, b$, ensures the following convergence results, $\mathcal{T}^\varepsilon(F_l(c_l^\varepsilon)) \rightharpoonup F_l(c_l)$ in $L^2(\Omega_T \times Y_j)$, for $l = e, i$, and $\mathcal{T}^\varepsilon(G_e(c_e^\varepsilon, r_f^\varepsilon, r_b^\varepsilon)) \rightharpoonup G_e(c_e, r_f, r_b)$, $\mathcal{T}^\varepsilon(F_f(r_f^\varepsilon, r_b^\varepsilon)) \rightharpoonup F_f(r_f, r_b)$, $\mathcal{T}^\varepsilon(F_d(p_d^\varepsilon)) \rightharpoonup F_d(p_d)$, $\mathcal{T}^\varepsilon(G_d(r_b^\varepsilon, p_d^\varepsilon, p_a^\varepsilon)) \rightharpoonup G_d(r_b, p_d, p_a)$, $\mathcal{T}^\varepsilon(G_i(p_a^\varepsilon, c_i^\varepsilon)) \rightharpoonup G_i(p_a, c_i)$ in $L^2(\Omega_T \times \Gamma)$. These convergence results together with the properties of the unfolding operator

(c.f., Appendix B) imply the convergence of the nonlinear terms in the microscopic problem.

To complete the proof, we note that standard results for parabolic equations imply

$$\begin{aligned} \partial_t c_e &\in L^2(0, T; H^1(\Omega)'), \quad \partial_t c_i \in L^2((0, T) \times \Omega; H^1(Y_i)'), \\ \partial_t r_l, \partial_t p_s &\in L^2((0, T) \times \Omega; H^1(\Gamma)'), \text{ for } l = f, b \text{ and } s = d, a. \end{aligned}$$

Thus $c_e \in C([0, T]; L^2(\Omega))$, $c_i \in C([0, T]; L^2(\Omega \times Y_i))$, and $r_j, p_s \in C([0, T]; L^2(\Omega \times \Gamma))$, for $j = f, b$ and $s = d, a$. Taking ϕ_1, ψ_1 , and φ_1 such that $\phi_1(T, x) = 0$, $\psi_1(T, x, y) = 0$, and $\varphi_1(T, x, z) = 0$ for $x \in \Omega$, $y \in Y_i$, $z \in \Gamma$ and using the strong two-scale convergence of $c_{i,0}^\varepsilon(x)$ to $c_{i,1}(x)c_{i,2}(y)$, of $r_{j,0}^\varepsilon(x)$ to $r_{j,1}(x)r_{j,2}(y)$, and of $p_{s,0}^\varepsilon(x)$ to $p_{s,1}(x)p_{s,2}(y)$, for $j = f, b$ and $s = a, d$, we deduce that the initial conditions (4.5) are satisfied. \square

To design a multiscale numerical scheme for the macroscopic two-scale problem (4.3)–(4.5) we define our notion of weak solutions to the problem.

DEFINITION 4.4. *Weak solutions of the macroscopic problem (4.3)–(4.5) are functions*

$$\begin{aligned} c_e &\in L^2(0, T; H^1(\Omega)) \text{ with } \partial_t c_e \in L^2(0, T; H^1(\Omega)'), \\ c_i &\in L^2(0, T; L^2(\Omega; H^1(Y_i))) \text{ with } \partial_t c_e \in L^2(\Omega_T; H^1(Y_i)'), \\ r_l &\in L^2(0, T; L^2(\Omega; H^1(\Gamma))) \text{ with } \partial_t r_l \in L^2(\Omega_T; H^1(\Gamma)'), \quad l = f, b, \\ p_s &\in L^2(0, T; L^2(\Omega; H^1(\Gamma))) \text{ with } \partial_t p_s \in L^2(\Omega_T; H^1(\Gamma)'), \quad s = a, d, \end{aligned}$$

such that

$$\begin{aligned} (4.8) \quad &\langle \theta_e \partial_t c_e, \phi \rangle + \langle D_e^{\text{hom}}(x) \nabla c_e, \nabla \phi \rangle_{\Omega_T} = \langle \theta_e F_e(c_e), \phi \rangle_{\Omega_T} \\ &\quad - \left\langle \frac{1}{|Y|} \int_{\Gamma} G_e(c_e, r_f, r_b) d\sigma_y, \phi \right\rangle_{\Omega_T}, \\ &\langle \partial_t c_i, \psi \rangle + \langle D_i(y) \nabla_y c_i, \nabla_y \psi \rangle_{Y_i \times \Omega_T} = \langle F_i(c_i), \psi \rangle_{Y_i \times \Omega_T} + \langle G_i(p_a, c_i), \psi \rangle_{\Gamma \times \Omega_T}, \end{aligned}$$

and

$$\begin{aligned} (4.9) \quad &\langle \partial_t r_f, \chi \rangle + \langle D_f \nabla_{\Gamma} r_f, \nabla_{\Gamma} \chi \rangle_{\Gamma \times \Omega_T} \\ &\quad = \langle F_f(r_f, r_b) - G_e(c_e, r_f, r_b) - d_f r_f, \chi \rangle_{\Gamma \times \Omega_T}, \\ &\langle \partial_t r_b, \chi \rangle + \langle D_b \nabla_{\Gamma} r_b, \nabla_{\Gamma} \chi \rangle_{\Gamma \times \Omega_T} \\ &\quad = \langle G_e(c_e, r_f, r_b) - G_d(r_b, p_a, p_d) - d_b r_b, \chi \rangle_{\Gamma \times \Omega_T}, \\ &\langle \partial_t p_d, \chi \rangle + \langle D_d \nabla_{\Gamma} p_d, \nabla_{\Gamma} \chi \rangle_{\Gamma \times \Omega_T} \\ &\quad = \langle F_d(p_d) - G_d(r_b, p_a, p_d) - d_d p_d, \chi \rangle_{\Gamma \times \Omega_T}, \\ &\langle \partial_t p_a, \chi \rangle + \langle D_a \nabla_{\Gamma} p_a, \nabla_{\Gamma} \chi \rangle_{\Gamma \times \Omega_T} \\ &\quad = \langle G_d(r_b, p_a, p_d) - G_i(p_a, c_i) - d_a p_a, \chi \rangle_{\Gamma \times \Omega_T}, \end{aligned}$$

for all $\phi \in L^2(0, T; H^1(\Omega))$, $\psi \in L^2(\Omega_T; H^1(Y_i))$, and $\chi \in L^2(\Omega_T; H^1(\Gamma))$, where the initial conditions (4.5) are satisfied in the L^2 -sense.

Notice that the coupling between macroscopic and microscopic scales is given through c_e in the equations for r_f and r_b and through the reaction term in the equation for c_e .

5. Numerical scheme for the homogenised problem. In this section we present a robust numerical method for the simulation of the homogenised macroscopic model of Section 4, i.e., equations (4.3) and (4.4). We employ a tensor product finite element approach for the discretisation of the two-scale systems [38]. For the bulk-surface systems, we employ a piecewise linear bulk-surface finite element method. The method is based on the coupled bulk-surface finite element method proposed and analysed (for linear elliptic systems) in [13].

We define computational domains Ω_h , $Y_{h,e}$, $Y_{h,i}$ and Γ_h by requiring that Ω_h , $Y_{h,e}$ and $Y_{h,i}$ are polyhedral approximations to Ω , Y_e and Y_i respectively and we set $\Gamma_h = \partial Y_{h,i}$, i.e., Γ_h is the boundary of the polyhedral domain $Y_{h,i}$. We assume that Ω_h , $Y_{h,e}$ and $Y_{h,i}$ consist of the union of d dimensional simplices (triangles for $d = 2$ and tetrahedra for $d = 3$) and hence the faces of Γ_h are $d - 1$ dimensional simplices.

We define $\mathcal{S}_{h,\Omega}$, $\mathcal{S}_{h,i}$, $\mathcal{S}_{h,e}$ to be triangulations of Ω_h , $Y_{h,i}$ and $Y_{h,e}$ respectively and assume that each consists of closed non-degenerate simplices. We denote by h_Ω , $h_{Y,i}$, $h_{Y,e}$ and h_Γ the maximum diameter of the simplices in $\mathcal{S}_{h,\Omega}$, $\mathcal{S}_{h,i}$, $\mathcal{S}_{h,e}$ and Γ_h respectively. Furthermore, we assume the triangulation is such that for every $k \in \mathcal{S}_{h,i}$, $k \cap \Gamma_h$ consists of at most one face of k . We define bulk and surface finite element spaces as follows

$$\begin{aligned} \mathbb{V}_{h,\Omega} &= \{ \Phi \in C(\Omega_h) : \Phi|_k \in \mathbb{P}^1, \text{ for all } k \in \mathcal{S}_{h,\Omega} \}, \\ \mathbb{V}_{h,i} &= \{ \Phi \in C(Y_{h,i}) : \Phi|_k \in \mathbb{P}^1, \text{ for all } k \in \mathcal{S}_{h,i} \}, \\ \mathbb{V}_{h,e} &= \{ \Phi \in C(Y_{h,e}) : \Phi|_k \in \mathbb{P}^1, \text{ for all } k \in \mathcal{S}_{h,e} \}, \\ \mathbb{V}_{h,e}^\# &= \{ \Phi \in H_{\text{per}}^1(Y_{h,e}) \cap C(Y_{h,e}) : \Phi|_k \in \mathbb{P}^1, \text{ for all } k \in \mathcal{S}_{h,e} \}, \\ \mathbb{V}_{h,\Gamma} &= \{ \Phi \in C(\Gamma_h) : \Phi|_k \in \mathbb{P}^1, \text{ for all } r \in \mathcal{S}_{h,i} \text{ with } k = r \cap \Gamma_h \neq \emptyset \}, \end{aligned}$$

where $H_{\text{per}}^1(Y_{h,e})$ denotes the subspace of Y -periodic functions in $H^1(Y_{h,e})$. For the discretisation of the two-scale systems we define the tensor product spaces

$$\begin{aligned} \mathbb{W}_{h,i} &= \mathbb{V}_{h,i} \otimes \mathbb{V}_{h,\Omega}, \\ \mathbb{W}_{h,e} &= \mathbb{V}_{h,e} \otimes \mathbb{V}_{h,\Omega}, \\ \mathbb{W}_{h,e}^\# &= \mathbb{V}_{h,e}^\# \otimes \mathbb{V}_{h,\Omega}, \\ \mathbb{W}_{h,\Gamma} &= \mathbb{V}_{h,\Gamma} \otimes \mathbb{V}_{h,\Omega}. \end{aligned}$$

The scheme for the solution of the cell problems to obtain the diffusion tensor D^{hom} is, for $j = 1, \dots, n+1$ find $W^j \in \mathbb{W}_{h,e}^\#$ such that

$$\langle D_e(x, y)(\nabla_y W^j + e_j), \nabla_y \Phi \rangle_{Y_{h,e} \times \Omega_h} = 0$$

for all $\Phi \in \mathbb{W}_{h,e}$.

In order to propose a fully discrete scheme, we divide the time interval $[0, T]$ into N subintervals, $0 = t_0 < \dots < t_N = T$ and denote by $\tau := t_n - t_{n-1}$ the time step, for simplicity we assume a uniform timestep. We consistently use the following shorthand for a function of time: $f^n := f(t_n)$, we denote by $\bar{\partial}_\tau f^n := \tau^{-1}(f^n - f^{n-1})$. We propose an IMEX time-stepping method in which the reactions are treated explicitly and the diffusive terms implicitly. The fully discrete scheme may be written as, for $i = 1, \dots, N$, given

$$C_e^{n-1} \in \mathbb{V}_{h,\Omega}, \quad C_i^{n-1} \in \mathbb{W}_{h,i}, \quad R_f^{n-1}, R_b^{n-1}, P_d^{n-1}, P_a^{n-1} \in \mathbb{W}_{h,\Gamma},$$

find

$$C_e^n \in \mathbb{V}_{h,\Omega}, \quad C_i^n \in \mathbb{W}_{h,i}, \quad R_f^n, R_b^n, P_d^n, P_a^n \in \mathbb{W}_{h,\Gamma},$$

such that, for all $\Phi \in \mathbb{V}_{h,\Omega}$ and $\Psi \in \mathbb{W}_{h,i}$

$$\begin{aligned} & \langle \theta_e \bar{\partial}_\tau C_e^n, \Phi \rangle_{\Omega_h} + \langle D_{h,e}^{\text{hom}}(x) \nabla C_e^n, \nabla \Phi \rangle_{\Omega_h} \\ &= \left\langle \theta_e F_e(C_e^{n-1}) - \frac{1}{|Y|} \int_{\Gamma_h} G_e(C_e^{n-1}, R_f^{n-1}, R_b^{n-1}) d\sigma_y, \Phi \right\rangle_{\Omega_h}, \\ (5.1) \quad & \langle \bar{\partial}_\tau C_i^n, \Psi \rangle_{Y_{h,i} \times \Omega_h} + \langle D_i(y) \nabla_y C_i^n, \nabla_y \Psi \rangle_{Y_{h,i} \times \Omega_h} \\ &= \langle F_i(C_i^{n-1}), \Psi \rangle_{Y_{h,i} \times \Omega_h} + \langle G_i(P_a^{n-1}, C_i^{n-1}), \Psi \rangle_{\Gamma_h \times \Omega_h}, \end{aligned}$$

and for all $\Xi \in \mathbb{W}_{h,\Gamma}$,

$$\begin{aligned} & \langle \bar{\partial}_\tau R_f^n, \Xi \rangle_{\Gamma_h \times \Omega_h} + \langle D_f \nabla_{\Gamma_h} R_f^n, \nabla_{\Gamma_h} \Xi \rangle_{\Gamma_h \times \Omega_h} \\ &= \left\langle F_f(R_f^{n-1}, R_b^{n-1}) - G_e(C_e^{n-1}, R_f^{n-1}, R_b^{n-1}) - d_f R_f^n, \Xi \right\rangle_{\Gamma_h \times \Omega_h}, \\ & \langle \bar{\partial}_\tau R_b^n, \Xi \rangle_{\Gamma_h \times \Omega_h} + \langle D_b \nabla_{\Gamma_h} R_b^n, \nabla_{\Gamma_h} \Xi \rangle_{\Gamma_h \times \Omega_h} \\ (5.2) \quad &= \left\langle G_e(C_e^{n-1}, R_f^{n-1}, R_b^{n-1}) - G_d(R_b^{n-1}, P_d^{n-1}, P_a^{n-1}) - d_b R_b^n, \Xi \right\rangle_{\Gamma_h \times \Omega_h}, \\ & \langle \bar{\partial}_\tau P_d^n, \Xi \rangle_{\Gamma_h \times \Omega_h} + \langle D_d \nabla_{\Gamma_h} P_d^n, \nabla_{\Gamma_h} \Xi \rangle_{\Gamma_h \times \Omega_h} \\ &= \left\langle F_d(P_d^{n-1}) - G_d(R_b^{n-1}, P_d^{n-1}, P_a^{n-1}) - d_d P_d^n, \Xi \right\rangle_{\Gamma_h \times \Omega_h}, \\ & \langle \bar{\partial}_\tau P_a^n, \Xi \rangle_{\Gamma_h \times \Omega_h} + \langle D_a \nabla_{\Gamma_h} P_a^n, \nabla_{\Gamma_h} \Xi \rangle_{\Gamma_h \times \Omega_h} \\ &= \left\langle G_d(R_b^{n-1}, P_d^{n-1}, P_a^{n-1}) - G_i(P_a^{n-1}, C_i^{n-1}) - d_a P_a^n, \Xi \right\rangle_{\Gamma_h \times \Omega_h}. \end{aligned}$$

Remark 5.1 (Comments on the implementation). The explicit treatment of the reaction terms results in fully decoupled systems of linear equations to be solved at each time-step. Moreover, we use mass lumping for the approximation, this has two main advantages in the context of the present study. Firstly, lumping is equivalent to employing a nodal quadrature rule [51], this allows us to interpret the two-scale systems as parameterised systems with the macroscopic variable playing the role of a parameter that may be solved independently and in parallel at each node of the macroscopic triangulation $\mathcal{S}_{h,\Omega}$. Secondly, the use of lumping and the fact that the system matrices do not change during the time evolution allows an efficient implementation in which virtually no assembly needs to be carried out on each time-step.

6. Benchmark computations. We now carry out some benchmark simulations to illustrate the observed convergence rate of the numerical scheme proposed in Section 5. We set $\Omega = [-0.5, 0.5]^2$ and Y_i to be a disc of radius 1. For benchmarking we consider the following system

$$\begin{aligned} & \partial_t c_e - \Delta c_e = - \int_{\Gamma} G_e(c_e, r_f, p_a) d\sigma_y + f_1 && \text{in } \Omega_T, \\ & \nabla c_e \cdot \nu = 0 && \text{on } (\partial\Omega)_T, \\ (6.1) \quad & \partial_t c_i - \Delta_y c_i = f_2 && \text{in } \Omega_T \times Y_i, \\ & \nabla_y c_i \cdot \nu = G_i(p_a, c_i) && \text{on } \Omega_T \times \Gamma, \\ & \partial_t r_f - \Delta_{\Gamma,y} r_f = -G_e(c_e, r_f, p_a) + f_3 && \text{on } \Omega_T \times \Gamma, \\ & \partial_t p_a - \Delta_{\Gamma,y} p_a = G_e(c_e, r_f, p_a) - G_i(p_a, c_i) + f_4 && \text{on } \Omega_T \times \Gamma, \end{aligned}$$

with

$$G_e(c_e, r_f, p_a) = c_e r_f - p_a \quad \text{and} \quad G_i(p_a, c_i) = p_a - c_i.$$

The source terms $f_1(x, t)$, $f_2(x, y, t)$, $f_3(x, z, t)$ and $f_4(x, z, t)$ for $x \in \Omega$, $y \in Y_i$, $z \in \Gamma$ and $t \in [0, T]$ are determined such that the exact solution to (6.1) is

$$c_e(x, t) = \cos(\pi t) e^{-10|x|^2}, c_i(x, y, t) = \left(1 + |x|^2\right) e^{-4t(y_1 y_2)^2} \quad \text{for } x \in \Omega, y \in Y_i$$

and

$$r_f(x, z, t) = p_a(x, z, t) = \left(5 + 5|x|^2\right) e^{-4t(z_1 z_2)^2}, \quad \text{for } x \in \Omega, z \in \Gamma$$

and we set as the end time $T = 0.25$.

In the numerical method we use the interpolant of the source terms into the appropriate finite element space. We consider a series of refinements of the meshes with $\tau \sim h^2$ where $h := \max\{h_\Gamma, h_{Y,i}, h_\Omega\}$. In particular we consider a series of uniform refinements of the bulk and surface meshes with mesh sizes as given in Table 1.

h_Γ	0.765	0.390	0.196	0.098	0.049
$h_{Y,i}$	1.000	0.571	0.305	0.157	0.080
h_Ω	1.000	0.500	0.250	0.125	0.063

Table 1: Mesh sizes for the benchmarking study of Section 6.

We denote by e_{c_e} , e_{c_i} , e_r and e_p the errors in the approximation of c_e , c_i , r_f and p_a respectively. In order to investigate the behaviour of the scheme we report on the experimental order of convergence (EOC) which provides a numerical measure of the convergence rate. For a series of uniform refinements of a triangulation $\{\mathcal{S}_{h,i}\}_{i=0,\dots,N}$, denoting by $\{h_i\}_{i=0,\dots,N}$, $\{e_i\}_{i=0,\dots,N}$ the corresponding maximum mesh-size and the corresponding error respectively, then the EOC is given by

$$\text{EOC}_i(e_{i,i+1}, h_{i,i+1}) := \ln(e_{i+1}/e_i) / \ln(h_{i+1}/h_i).$$

Figure 2 shows the errors and the corresponding EOCs. The convergence rates appear optimal with first order convergence in the energy norm and second order convergence (as $\tau \sim h^2$) in the L^2 norm.

An analysis of the numerical method is beyond the scope of the present work. We believe that combining the techniques developed in [13] for the analysis of finite element schemes for bulk-surface equations, [22] which deals with multiscale finite element methods and [26] which proves error bounds for IMEX approximations of semilinear systems, it should be possible to prove optimal error bounds for our method that reflect the rates observed numerically in Figure 2.

7. Parameterisation and numerical solutions for a biologically relevant model. We now present and simulate a biologically relevant model, the model considered in this section is related to the Langmuir-Hinshelwood mechanism for signalling processes at the level of a single cell considered in [18], and in particular we take the majority of our parameters from said work. We make the assumption that all the parameters are independent of the microscopic variable and state the parameter values we use in the microscopic model (2.1)–(2.5) along with the source of the parameter value in Table 2. In order to keep the model as simple as

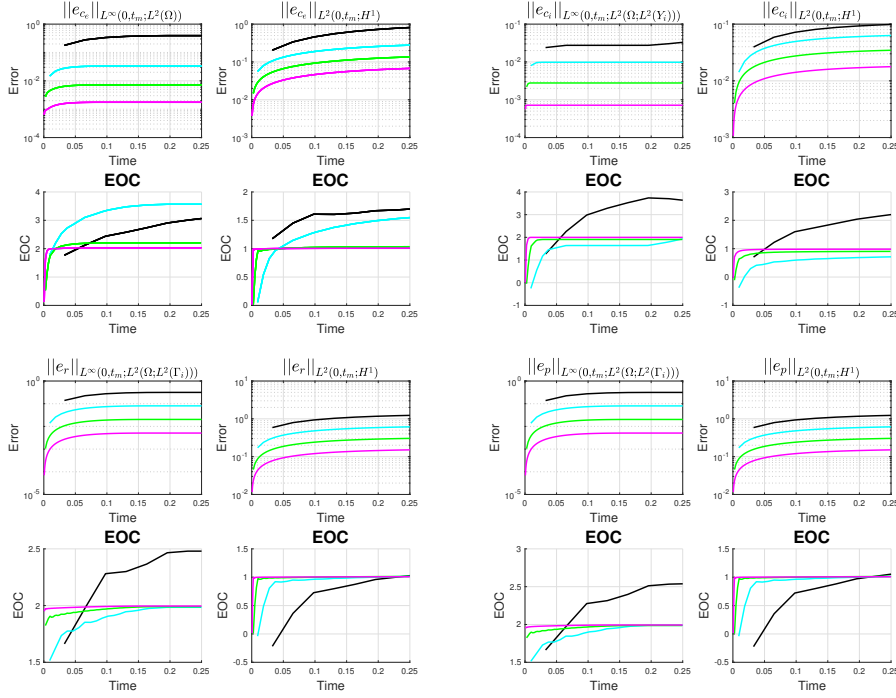


Fig. 2: Errors in the $L^2(H^1)$ and $L^\infty(L^2)$ norms for a series of mesh refinements (c.f., Table 1) with $\tau \sim h^2$ and experimental order of convergence. The observed convergence rates appear optimal.

possible whilst still illustrating the key phenomena captured by the model, we assume there is no production or linear degradation of any of the species, i.e., we set $F_e(c_e) = F_i(c_i) = F_f(r_f, r_b) = F_d(p_d) = 0$ and $d_k = 0$ for $k = b, f, a, d$.

The dependent and independent variables of the microscopic model and their associated units are as given in Table 3. Finally, in order to ensure there is some ligand present in the system, we set $\partial\Omega_D$ to be a Dirichlet boundary such that the boundary condition (2.5) becomes

$$\begin{aligned} c_e^\varepsilon &= \hat{c}_e & \text{on } \partial\Omega_D, \quad t \geq 0, \\ D_e^\varepsilon(x) \nabla c_e^\varepsilon \cdot \nu &= 0 & \text{on } \partial\Omega \setminus \partial\Omega_D, \quad t > 0, \end{aligned}$$

where we set $\hat{c}_e = 10^{-4} \text{ mol/m}^3$, c.f., [18]. Taking $\varepsilon = 10^{-3}$ we introduce the characteristic scales

$$(7.1) \quad \begin{aligned} \hat{t} &= 10^3 \text{ s}, \quad \hat{x} = 10^{-2} \text{ m}, \quad \hat{r} = \hat{r}_l = \hat{p}_k = 10^{-9} \frac{\text{mol}}{\text{m}^2}, \\ \hat{c} &= \hat{c}_e = \hat{c}_i = \frac{\hat{r}}{\varepsilon \hat{x}} = 10^{-4} \frac{\text{mol}}{\text{m}^3}, \end{aligned}$$

Parameter	Value	Source
a_e	$10^3 (\text{mol}/\text{m}^3)^{-1} \text{s}^{-1}$	[18]
b_e	$5 \cdot 10^{-3} \text{s}^{-1}$	[18]
a_i	$10^{-2} (\frac{\text{molecules}}{\mu\text{m}^2})^{-1} \text{s}^{-1} = 6 \cdot 10^9 (\text{mol}/\text{m}^2)^{-1} \text{s}^{-1}$	[18]
b_i	10^{-2}s^{-1}	[18]
γ_i	$2 \cdot 10^{-3} \text{s}^{-1}$	[18]
κ_i	10^{-8}m s^{-1}	[18]
D_e	$10^{-9} \text{m}^2 \text{s}^{-1}$	[30]
D_i	$10^{-11} \text{m}^2 \text{s}^{-1}$	[49]
$D_k, \quad k = b, f, a, d$	$10^{-15} \text{m}^2 \text{s}^{-1}$	[30]

Table 2: Parameters used for the microscopic model and sources for the parameter estimates.

x	t	c_e	c_i	r_f, r_b	p_d, p_a
m	s	mol/m ³	mol/m ³	mol/m ²	mol/m ²

Table 3: Variables of microscopic model and associated units.

where $l = f, b$ and $k = a, d$, and then the dimensionless parameters are given by

$$\begin{aligned}
(7.2) \quad & D_e^* = D_e \hat{t} / (\hat{x})^2 = 10^{-2}, \quad \varepsilon^2 D_i^* = D_i \hat{t} / (\hat{x})^2 = 10^{-5}, \quad D_i^* = 10 \\
& \varepsilon^2 D_l^* = D_l \hat{t} / (\hat{x})^2 = 10^{-8}, \quad D_l^* = 10^{-2}, \quad l = f, b, d, a, \\
& \varepsilon b_e^* = \frac{\hat{t}}{\hat{x}} \frac{\hat{r}_b}{\hat{c}} b_e = 5 \cdot 10^{-3}, \quad \varepsilon a_e^* = \frac{\hat{t} \hat{r}_f}{\hat{x}} a_e = 0.1, \quad b_e^* = 5, \quad a_e^* = 100, \\
& \varepsilon \gamma_i^* = \frac{\hat{t}}{\hat{x}} \frac{\hat{p}_a}{\hat{c}_i} \gamma_i = 2 \cdot 10^{-3}, \quad \varepsilon \kappa_i^* = \frac{\hat{t}}{\hat{x}} \kappa_i = 10^{-3}, \quad \gamma_i^* = 2, \quad \kappa_i^* = 1, \\
& a_i^* = a_i \hat{p}_d \hat{t} = 6 \cdot 10^3, \quad b_i^* = b_i \hat{t} = 10.
\end{aligned}$$

Notice that we also have $a_e^* = a_e \hat{c} \hat{t} = 100$, $b_e^* = b_e \hat{t} = 5$, and $\gamma_i^* = \gamma_i \hat{t} = 2$, $\kappa_i^* = \frac{\hat{t} \hat{c}_i}{\hat{p}_d} \kappa_i = 1$, which is consistent with scaling above. Following the derivation of the two-scale macroscopic model outlined in Section 4 we obtain the following dimensionless homogenised system

$$\begin{aligned}
(7.3) \quad & \theta_e \partial_t c_e - \nabla \cdot (D_e^{\text{hom}} \nabla c_e) = \frac{1}{|Y|} \int_{\Gamma} (b_e^* r_b - a_e^* c_e r_f) d\sigma_y \quad \text{in } \Omega, \\
& c_e = 1 \quad \text{on } \partial\Omega_D, \\
& D_e^{\text{hom}} \nabla c_e \cdot \nu = 0 \quad \text{on } \partial\Omega / \partial\Omega_D, \\
& \partial_t c_i - \nabla_y \cdot (D_i^* \nabla_y c_i) = 0 \quad \text{in } \Omega \times Y_i, \\
& D_i^* \nabla_y c_i \cdot \nu = \gamma_i^* p_a - \kappa_i^* c_i \quad \text{in } \Omega \times \Gamma,
\end{aligned}$$

where $\theta_e = |Y_e|/|Y|$, and $D_{e,ij}^{\text{hom}} = |Y|^{-1} \int_{Y_e} [D_e^* \nabla_y w^j(y)]_i dy$ and w^j are

solutions of the unit cell problems

$$(7.4) \quad \begin{aligned} \operatorname{div}_y(D_e^*(\nabla_y w^j + e_j)) &= 0 \quad \text{in } Y_e, \quad \int_{Y_e} w^j(y) dy = 0, \\ D_e^*(\nabla_y w^j + e_j) \cdot \nu &= 0 \quad \text{on } \Gamma, \quad w^j \text{ } Y\text{-periodic,} \end{aligned}$$

together with the dynamics of receptors on the cell membrane $\Omega \times \Gamma$

$$(7.5) \quad \begin{aligned} \partial_t r_f - \nabla_{\Gamma,y} \cdot (D_f^* \nabla_{\Gamma,y} r_f) &= -a_e^* c_e r_f + b_e^* r_b, \\ \partial_t r_b - \nabla_{\Gamma,y} \cdot (D_b^* \nabla_{\Gamma,y} r_b) &= a_e^* c_e r_f - b_e^* r_b - a_i^* r_b p_d + b_i^* p_a, \\ \partial_t p_d - \nabla_{\Gamma,y} \cdot (D_d^* \nabla_{\Gamma,y} p_d) &= -a_i^* r_b p_d + b_i^* p_a, \\ \partial_t p_a - \nabla_{\Gamma,y} \cdot (D_a^* \nabla_{\Gamma,y} p_a) &= a_i^* r_b p_d - b_i^* p_a - \gamma_i^* p_a + \kappa_i^* c_i. \end{aligned}$$

The dimensionless parameter values are

$$(7.6) \quad \begin{aligned} D_e^* &= 10^{-2}, \quad D_i^* = 10, \quad D_f^* = D_b^* = D_d^* = D_a^* = 10^{-2}, \\ a_e^* &= 100, \quad b_e^* = 5, \quad a_i^* = 6 \cdot 10^3, \quad b_i^* = 10, \quad \gamma_i^* = 2, \quad \kappa_i^* = 1. \end{aligned}$$

Scaling the initial conditions appropriately yields the nondimensional initial values

$$(7.7) \quad \begin{aligned} c_{i0}^*(x, y) &= 1 + c_{i,1}(x) c_{i,2}(y), \\ r_{f0}^*(x, z) &= 0.17(1 + r_{f,1}(x) r_{f,2}(z)), \quad p_{d0}^*(x, z) = 0.065(1 + p_{d,1}(x) p_{d,2}(z)), \end{aligned}$$

for $x \in \Omega$, $y \in Y_i$ and $z \in \Gamma$, with all the remaining initial conditions taken to be zero. The functions c_{i0}^* , r_{f0}^* and p_{d0}^* correspond to scaled, nonnegative perturbations of the initial conditions

$$(7.8) \quad c_{i0} = 10^{-7} \text{ M} = 10^{-4} \frac{\text{mol}}{\text{m}^3}, \quad r_{f0} = 17 \cdot 10^{-11} \frac{\text{mol}}{\text{m}^2}, \quad p_{d0} = 6.5 \cdot 10^{-11} \frac{\text{mol}}{\text{m}^2},$$

considered in [18].

7.1. Simulations of macroscopic model in biologically relevant regimes.

We illustrate the influence that the geometry of the periodic cell in which we solve for the effective homogenised diffusion tensor D^{hom} as well as the associated geometry of the (biological) cells Y_i and membranes Γ have on the macroscopic dynamics of signalling molecules (ligands). To this end we consider two different geometries for the microstructure, specifically we let $Y = [-2, 2]^2$ and consider either elliptical cells with

$$Y_i = \{x \in Y \mid 0.26x_1^2 + 5x_2^2 < 1\},$$

i.e., an ellipse centred at $(0, 0)$ with major and minor axes of approximate length 1.96 and 0.45 respectively or cells whose shape is defined by

$$(7.9) \quad Y_i = \{x \in Y \mid (x_1 + 0.2 - x_2^2)^2 + x_2^2 < 1\}.$$

To obtain the homogenised diffusion tensor we solve the cell problems corresponding to (7.4) on $Y_e = [-2, 2]^2 / Y_i$ for the two different cell geometries. For the elliptical cell geometry we used a mesh with 1039514 DOFs and for the other cell geometry we used a mesh with 1008834 DOFs. Figure 3 shows the numerical simulation results for the solution w^2 of the 'unit cell' problems (7.4) on the two different geometries. The resulting homogenised diffusion tensor is given by

$$D_{h,e}^{\text{hom}} = \begin{bmatrix} 8.167 \cdot 10^{-3} & 0 \\ 0 & 1.841 \cdot 10^{-3} \end{bmatrix}$$

for the case of the ellipse and

$$D_{h,e}^{\text{hom}} = \begin{bmatrix} 6.556 \cdot 10^{-3} & 0 \\ 0 & 6.149 \cdot 10^{-3} \end{bmatrix}$$

for the geometry specified in (7.9). As expected due to the large aspect ratio of the ellipse the resulting homogenised diffusion tensor exhibits stronger anisotropy than for the other cell shape. For the tissue we set $\Omega = [0, 0.1]^2$ and take

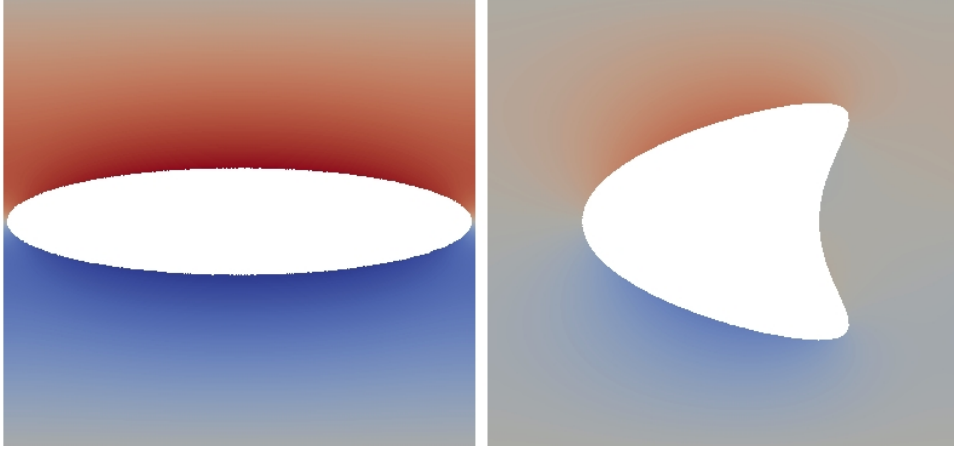


Fig. 3: Solutions w^2 of the cell problem (7.4) for the two different Y_e domains considered.

$$\partial\Omega_D = \{x \in \partial\Omega \mid \max\{x_1, x_2\} < 5 \cdot 10^{-2}\},$$

modelling a constant source of ligands from the south west corner of the domain. As mentioned above on the remainder of the boundary $\partial\Omega$ we consider zero-flux boundary condition for c_e . For the initial data we set the perturbations c.f., (7.7) to be of the form

$$\begin{aligned} c_{i,1}(x)c_{i,2}(y) &= f_{c_{i0}}(x, y) = 0.95 \sin\left(\pi\left(2y_1 + \frac{y_2}{2}\right)\right) \sin(5\pi|x|), \\ r_{f,1}(x)r_{f,2}(y) &= f_{r_{f0}}(x, y) = 0.95 \cos(\pi(y_1 + 4y_2)) \cos(30\pi|x|), \\ p_{d,1}(x)p_{d,2}(y) &= f_{p_{d0}}(x, y) = 0.95 \cos\left(\pi\left(2y_1 + \frac{y_2}{2}\right)\right) \cos(10\pi|x|), \end{aligned}$$

for $x \in \Omega$ and $y \in Y$. For the approximation we used a triangulation Ω_h with 1089 DOFs, the triangulation $Y_{h,i}$ of the ellipse had 81 DOFs and the triangulation $Y_{h,i}$ of the domain given by (7.9) had 89 DOFs, the induced surface triangulations Γ_h had 32 and 33 DOFs respectively. For the timestep we used a value of $2 \cdot 10^{-3}$.

Figures 4 and 5 show results of the simulation at $t = 10, 100, 200$ and 250 with the elliptical cell geometry whilst Figure 6 shows results of the simulation at the same times with the cell geometry given by (7.9). In each Figure we also include the microscopic solutions at the DOFs with macroscopic coordinates $(0, 0)$, $(0.05, 0.05)$ and $(0.1, 0.1)$ with the macroscopic DOF associated with each set of microscopic results indicated by a grey line in the Figure to the corresponding point in the macroscopic domain. Focusing on the differences between the two sets of results, we see that

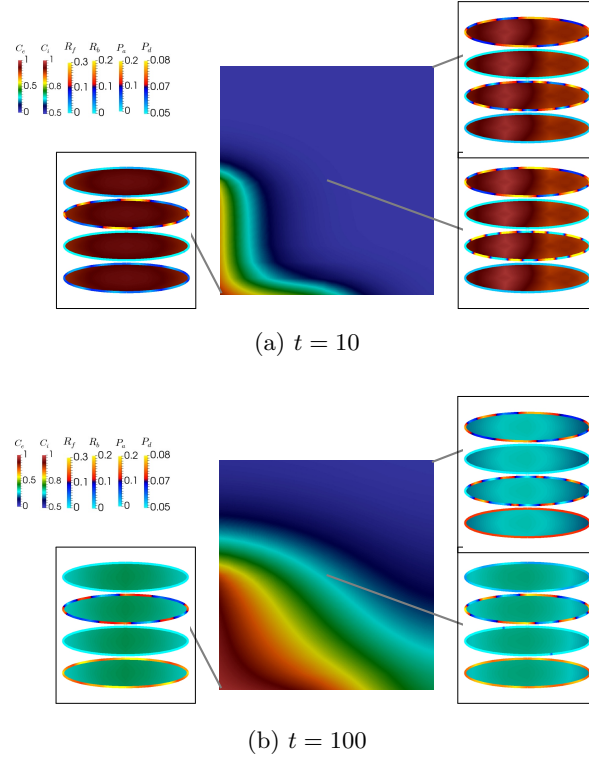


Fig. 4: Results of the simulation of Section 7 with the elliptical cell geometry. The inset in each subfigure show the microscopic solutions at the corresponding macroscopic DOF (grey line). The macroscopic domain is shaded by C_e whilst in each inset the cell interior is shaded by C_i and reading from top to bottom, the membrane is shaded by R_f, R_b, P_d and P_a respectively. For further details see text.

the strongly anisotropic homogenised diffusion tensor associated with the elliptical cell geometry leads to faster transport in the horizontal direction and slower vertical transport. As a result for $t = 200$, see Figure 5a, there are very few bound receptors present on the cell at the macroscopic point $(0.1, 0.1)$ and it is only by $t = 250$ that bound receptors are clearly visible on this cell. On the other hand the almost isotropic homogenised diffusion tensor associated with the cell geometry specified in (7.9) leads to equally fast vertical and horizontal transport and by $t = 200$ there are clearly a large number of bound receptors present on the cell membrane at the macroscopic point $(0.1, 0.1)$, c.f., Figure 6c. More generally, in both cases we see significant heterogeneity at the microscopic level in the concentrations of the different membrane resident species at different times during the simulation motivating the multiscale modelling approach we employ.

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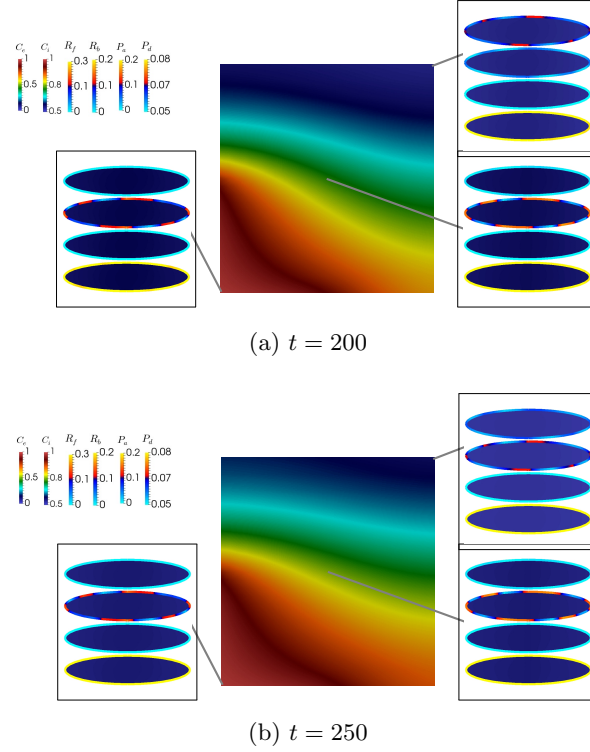


Fig. 5: Results of the simulation of Section 7 with the elliptical cell geometry. The inset in each subfigure show the microscopic solutions at the corresponding macroscopic DOF (grey line). The macroscopic domain is shaded by C_e whilst in each inset the cell interior is shaded by C_i and reading from top to bottom, the membrane is shaded by R_f , R_b , P_d and P_a respectively. For further details see text.

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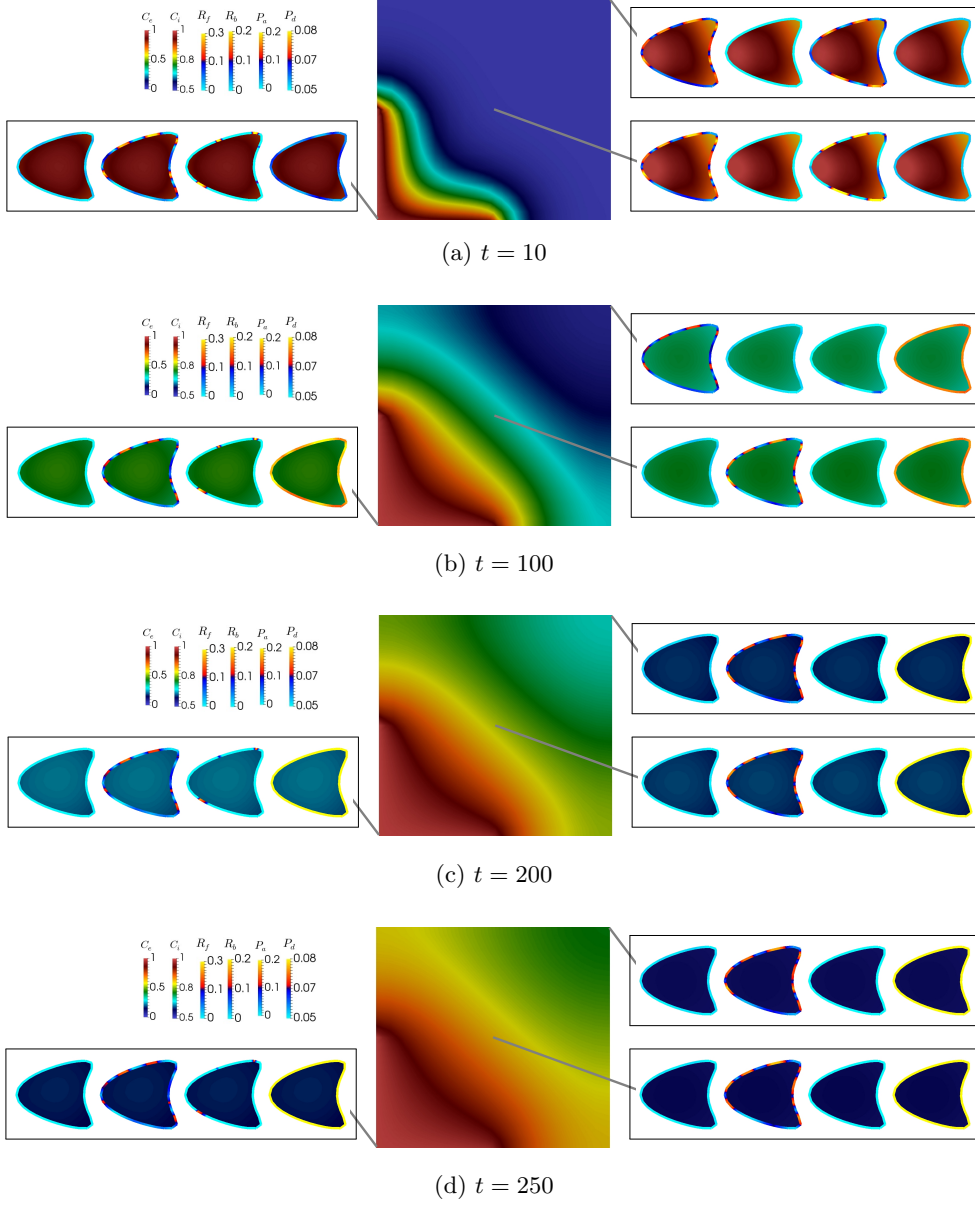


Fig. 6: Results of the simulation of Section 7 with the cell geometry given by (7.9). The inset in each subfigure show the microscopic solutions at the corresponding macroscopic DOF (grey line). The macroscopic domain is shaded by C_e whilst in each inset the cell interior is shaded by C_i and reading from left to right, the membrane is shaded by R_f, R_b, P_d and P_e respectively. For further details see text.

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Appendix A. Generalised trace inequality. The trace inequality for $v \in W^{1,q}(Y_l)$, with $1 < q < \infty$ and $l = e, i$, reads

$$(A.1) \quad \|v\|_{L^r(\Gamma)} \leq \mu [\|v\|_{L^q(Y_l)}^{1-\lambda} \|v\|_{W^{1,q}(Y_l)}^\lambda + \|v\|_{L^q(Y_l)}^{(1-1/r)(1-\lambda)} \|v\|_{W^{1,q}(Y_l)}^{1/r+\lambda(1-1/r)}]$$

for $\lambda = \frac{\dim(Y_l)(r-q)}{q(r-1)}$ and $\mu = \mu(r, q, Y_l) > 0$, see e.g. [17].

Appendix B. Two-scale convergence and periodic unfolding operator.

We recall the definition and some properties of two-scale convergence and the unfolding operator.

DEFINITION B.1 (Two-scale convergence). [4, 31, 44] A sequence $\{u^\varepsilon\}$ in $L^p(\Omega)$,

with $1 < p < \infty$, is two-scale convergent to $u \in L^p(\Omega \times Y)$ if

$$\lim_{\varepsilon \rightarrow 0} \int_{\Omega} u^{\varepsilon}(x) \phi\left(x, \frac{x}{\varepsilon}\right) dx = \int_{\Omega \times Y} u(x, y) \phi(x, y) dy dx$$

for any $\phi \in L^q(\Omega; C_{\text{per}}(Y))$, with $1/p + 1/q = 1$.

THEOREM B.2. [5, 43] Let $\{v^{\varepsilon}\} \subset L^2(\Gamma^{\varepsilon})$ satisfies $\varepsilon \|v^{\varepsilon}\|_{L^2(\Gamma^{\varepsilon})}^2 \leq C$, then there exists a two-scale limit $v \in L^2(\Omega; L^2(\Gamma))$ such that, up to a subsequence, v^{ε} two-scale converge to v in the sense that

$$\lim_{\varepsilon \rightarrow 0} \varepsilon \int_{\Gamma^{\varepsilon}} v^{\varepsilon}(x) \phi\left(x, \frac{x}{\varepsilon}\right) d\sigma^{\varepsilon} = \int_{\Omega \times \Gamma} v(x, y) \phi(x, y) d\sigma_y dx$$

for any $\phi \in C_0(\Omega; C_{\text{per}}(Y))$.

LEMMA B.3 (Two-scale compactness [4, 5, 44]).

- i. If $\{u^{\varepsilon}\}$ is bounded in $L^2(\Omega)$, there exists a subsequence (not relabelled) such that $u^{\varepsilon} \rightharpoonup u$ two-scale as $\varepsilon \rightarrow 0$ for some function $u \in L^2(\Omega \times Y)$.
- ii. If $u^{\varepsilon} \rightharpoonup u$ weakly in $H^1(\Omega)$ then $u^{\varepsilon} \rightharpoonup u$ and $\nabla u^{\varepsilon} \rightharpoonup \nabla u + \nabla_y u_1$ two-scale, where $u_1 \in L^2(\Omega; H_{\text{per}}^1(Y)/\mathbb{R})$.
- iii. If $\|u^{\varepsilon}\|_{H^1(\Omega^{\varepsilon})} \leq C$ and $[u^{\varepsilon}]^{\sim}$ and $[\nabla u^{\varepsilon}]^{\sim}$ are extensions by zero from Ω_e^{ε} into Ω of u^{ε} and ∇u^{ε} respectively, then, up to a subsequence, $[u^{\varepsilon}]^{\sim}$ and $[\nabla u^{\varepsilon}]^{\sim}$ converge two-scale to $u\chi$ and $[\nabla u + \nabla_y u_1]\chi$ respectively, where $\chi = \chi(y)$ is the characteristic function of Y_e , $u \in H^1(\Omega)$ and $u_1 \in L^2(\Omega; H_{\text{per}}^1(Y_e)/\mathbb{R})$.
- iv. Let $\{w^{\varepsilon}\} \subset H^1(\Gamma^{\varepsilon})$ satisfies

$$\varepsilon \|w^{\varepsilon}\|_{L^2(\Gamma^{\varepsilon})}^2 + \varepsilon \|\varepsilon \nabla_{\Gamma} w^{\varepsilon}\|_{L^2(\Gamma^{\varepsilon})}^2 \leq C,$$

then there exists a function $w \in L^2(\Omega; H^1(\Gamma))$ such that, up to a subsequence, w^{ε} and $\varepsilon \nabla_{\Gamma} w^{\varepsilon}$ two-scale converge to w and $\nabla_{\Gamma, y} w$, respectively.

To define the unfolding operator, let $[z]$ for any $z \in \mathbb{R}^d$ denote the unique combination $\sum_{i=1}^d k_i e_i$ with $k \in \mathbb{Z}^d$, such that $z - [z] \in Y$, where e_i is the i th canonical basis vector of \mathbb{R}^d .

DEFINITION B.4 (Unfolding operator [10]). Let $p \in [1, \infty]$ and $\phi \in L^p(\Omega)$. The unfolding operator $\mathcal{T}^{\varepsilon}$ is defined by $\mathcal{T}^{\varepsilon}(\phi) \in L^p(\Omega \times Y)$, where

$$\mathcal{T}^{\varepsilon}(\phi)(x, y) = \begin{cases} \phi\left(\varepsilon \left[\frac{x}{\varepsilon}\right] + \varepsilon y\right) & \text{for a.e. } (x, y) \in \tilde{\Omega}^{\varepsilon} \times Y, \\ 0 & \text{for a.e. } x \in \Omega \setminus \tilde{\Omega}^{\varepsilon}, y \in Y, \end{cases}$$

with $\tilde{\Omega}^{\varepsilon} = \bigcup_{\xi \in \Xi^{\varepsilon}} \varepsilon(Y + \xi)$.

For $\psi \in L^p(\tilde{\Omega}_l^{\varepsilon})$, with $l = e, i$, the unfolding operator $\mathcal{T}_{Y_l}^{\varepsilon}$ is defined by

$$\mathcal{T}_{Y_l}^{\varepsilon}(\psi)(x, y) = \begin{cases} \psi\left(\varepsilon \left[\frac{x}{\varepsilon}\right] + \varepsilon y\right) & \text{for a.e. } (x, y) \in \tilde{\Omega}^{\varepsilon} \times Y_l, \\ 0 & \text{for a.e. } x \in \Omega \setminus \tilde{\Omega}^{\varepsilon}, y \in Y_l, \end{cases}$$

and $\mathcal{T}_{Y_l}^{\varepsilon}(\psi) \in L^p(\Omega \times Y_l)$.

For $\psi \in L^p(\Gamma^{\varepsilon})$ the boundary unfolding operator $\mathcal{T}_{\Gamma}^{\varepsilon}$ is defined by

$$\mathcal{T}_{\Gamma}^{\varepsilon}(\psi)(x, y) = \begin{cases} \psi\left(\varepsilon \left[\frac{x}{\varepsilon}\right] + \varepsilon y\right) & \text{for a.e. } (x, y) \in \tilde{\Omega}^{\varepsilon} \times \Gamma, \\ 0 & \text{for a.e. } x \in \Omega \setminus \tilde{\Omega}^{\varepsilon}, y \in \Gamma, \end{cases}$$

and $\mathcal{T}_\Gamma^\varepsilon(\psi) \in L^p(\Omega \times \Gamma)$.

For any function ψ defined on Ω_l^ε , for $l = e, i$, we have $\mathcal{T}_{Y_l}^\varepsilon(\psi) = \mathcal{T}^\varepsilon([\psi]^\sim)|_{\Omega \times Y_l}$, with $[\psi]^\sim$ denoting extension of ψ by zero into $\Omega \setminus \Omega_l^\varepsilon$, whereas for ϕ defined on Ω , it holds that $\mathcal{T}_{Y_l}^\varepsilon(\phi|_{\Omega_l^\varepsilon}) = \mathcal{T}^\varepsilon(\phi)|_{\Omega \times Y_l}$.

The following result relates two-scale convergence and weak convergence involving the unfolding operator.

PROPOSITION B.5 ([11]). *Let $\{\psi^\varepsilon\}$ be a bounded sequence in $L^p(\Omega)$ for some $1 < p < \infty$. Then the following assertions are equivalent:*

- i. $\{\mathcal{T}^\varepsilon(\psi^\varepsilon)\}$ converges weakly to ψ in $L^p(\Omega \times Y)$.
- ii. $\{\psi^\varepsilon\}$ converges two-scale to ψ , $\psi \in L^p(\Omega \times Y)$.

We have the following properties of the periodic unfolding operator and the boundary unfolding operator:

$$\begin{aligned}
 & \mathcal{T}_{Y_l}^\varepsilon(F(u, v)) = F(\mathcal{T}_{Y_l}^\varepsilon(u), \mathcal{T}_{Y_l}^\varepsilon(v)), \quad \mathcal{T}_{Y_l}^\varepsilon(v(t, x/\varepsilon)) = v(t, y), \quad x \in \Omega_l^\varepsilon, y \in Y_l, \\
 & \mathcal{T}_\Gamma^\varepsilon(F(u, v)) = F(\mathcal{T}_\Gamma^\varepsilon(u), \mathcal{T}_\Gamma^\varepsilon(v)), \quad \mathcal{T}_\Gamma^\varepsilon(v(t, x/\varepsilon)) = v(t, y), \quad x \in \Omega_l^\varepsilon, y \in \Gamma, t > 0, \\
 & |Y| \langle v, u \rangle_{\Omega_{i,T}^\varepsilon} = \langle \mathcal{T}_{Y_i}^\varepsilon(v), \mathcal{T}_{Y_i}^\varepsilon(u) \rangle_{Y_i \times \Omega_T}, \quad |Y| \varepsilon \langle v, u \rangle_{\Gamma_T^\varepsilon} = \langle \mathcal{T}_\Gamma^\varepsilon(v), \mathcal{T}_\Gamma^\varepsilon(u) \rangle_{\Gamma \times \Omega_T}, \\
 & \langle \mathcal{T}_{Y_e}^\varepsilon(v), \mathcal{T}_{Y_e}^\varepsilon(u) \rangle_{Y_e \times \Omega_T} = |Y| \langle v, u \rangle_{\Omega_{e,T}^\varepsilon} - |Y| \langle v, u \rangle_{(\Omega_\varepsilon \setminus \bar{\Omega}_\varepsilon)_T}, \\
 & \|\mathcal{T}_{Y_l}^\varepsilon(\phi)\|_{L^p(\Omega_T \times Y_l)} \leq |Y|^{\frac{1}{p}} \|\phi\|_{L^p(\Omega_{l,T}^\varepsilon)}, \\
 & \mathcal{T}_{Y_l}^\varepsilon : L^p(0, T; W^{1,p}(\Omega_l^\varepsilon)) \rightarrow L^p(\Omega_T; W^{1,p}(Y_l)), \\
 & \mathcal{T}_\Gamma^\varepsilon : L^p(0, T; W^{1,p}(\Gamma^\varepsilon)) \rightarrow L^p(\Omega_T; W^{1,p}(\Gamma)), \\
 & \varepsilon \mathcal{T}_{Y_l}^\varepsilon(\nabla u) = \nabla_y \mathcal{T}_{Y_l}^\varepsilon(u), \quad |Y| \langle \varepsilon^2 \nabla v, \nabla u \rangle_{\Omega_{i,T}^\varepsilon} = \langle \nabla_y \mathcal{T}_{Y_i}^\varepsilon(v), \nabla_y \mathcal{T}_{Y_i}^\varepsilon(u) \rangle_{Y_i \times \Omega_T}, \\
 & |Y| \varepsilon \langle \varepsilon^2 \nabla_\Gamma v, \nabla_\Gamma u \rangle_{\Gamma_T^\varepsilon} = \langle \nabla_{\Gamma,y} \mathcal{T}_\Gamma^\varepsilon(v), \nabla_{\Gamma,y} \mathcal{T}_\Gamma^\varepsilon(u) \rangle_{\Gamma \times \Omega_T}, \\
 & \|\mathcal{T}_\Gamma^\varepsilon(\psi)\|_{L^p(\Omega_T \times \Gamma)} \leq \varepsilon^{\frac{1}{p}} |Y|^{\frac{1}{p}} \|\psi\|_{L^p(\Gamma_T^\varepsilon)} \leq C(\|\psi\|_{L^p(\Omega_{i,T}^\varepsilon)} + \varepsilon \|\nabla \psi\|_{L^p(\Omega_{i,T}^\varepsilon)}),
 \end{aligned}
 \tag{B.1}$$

for $u, v \in L^2(0, T; H^1(\Omega_l^\varepsilon))$, where $l = e, i$, or $u, v \in L^2(0, T; H^1(\Gamma^\varepsilon))$, $\phi \in L^p(\Omega_{l,T}^\varepsilon)$, $\psi \in L^p(0, T; W^{1,p}(\Omega_l^\varepsilon))$ and F is any linear or nonlinear function, see e.g. [10, 11, 20].

We now collect some results on the convergence of the unfolding of sequences of functions.

LEMMA B.6 ([11]). *Let $1 \leq p < \infty$.*

- i. *If $\phi \in L^p(\Omega)$, then $\mathcal{T}^\varepsilon(\phi) \rightarrow \phi$ strongly in $L^p(\Omega \times Y)$.*
- ii. *Let $\{\psi^\varepsilon\} \subset L^p(\Omega)$, with $\psi^\varepsilon \rightarrow \psi$ strongly in $L^p(\Omega)$, then $\mathcal{T}^\varepsilon(\psi^\varepsilon) \rightarrow \psi$ strongly in $L^p(\Omega \times Y)$.*

THEOREM B.7 ([10, 20]).

- i. *Let $\{\psi^\varepsilon\}$ be a bounded sequence in $W^{1,p}(\Omega_e^\varepsilon)$, for some $1 < p < \infty$. Then there exist functions $\psi \in W^{1,p}(\Omega)$ and $\psi_1 \in L^p(\Omega; W_{\text{per}}^{1,p}(Y_e)/\mathbb{R})$ such that as $\varepsilon \rightarrow 0$, up to a subsequence,*

$$\begin{aligned}
 \mathcal{T}_{Y_e}^\varepsilon(\psi^\varepsilon) &\rightharpoonup \psi && \text{weakly in } L^p(\Omega; W^{1,p}(Y_e)), \\
 \mathcal{T}_{Y_e}^\varepsilon(\psi^\varepsilon) &\rightarrow \psi && \text{strongly in } L_{\text{loc}}^p(\Omega; W^{1,p}(Y_e)), \\
 \mathcal{T}_{Y_e}^\varepsilon(\nabla \psi^\varepsilon) &\rightharpoonup \nabla \psi + \nabla_y \psi_1 && \text{weakly in } L^p(\Omega \times Y_e).
 \end{aligned}$$

- ii. *Let $\{\phi^\varepsilon\} \subset W^{1,p}(\Omega_i^\varepsilon)$, for some $1 < p < \infty$, satisfies*

$$\|\phi^\varepsilon\|_{L^p(\Omega_i^\varepsilon)} + \varepsilon \|\nabla \phi^\varepsilon\|_{L^p(\Omega_i^\varepsilon)} \leq C.$$

Then there exists $\phi \in L^p(\Omega; W^{1,p}(Y_i))$ such that as $\varepsilon \rightarrow 0$, up to a subsequence,

$$\begin{aligned} \mathcal{T}_{Y_i}^\varepsilon(\phi^\varepsilon) &\rightharpoonup \phi && \text{weakly in } L^p(\Omega \times Y_i), \\ \varepsilon \mathcal{T}_{Y_i}^\varepsilon(\nabla \phi^\varepsilon) &\rightharpoonup \nabla_y \phi && \text{weakly in } L^p(\Omega \times Y_i). \end{aligned}$$

iii. Let $\{w^\varepsilon\} \subset H^1(\Gamma^\varepsilon)$ satisfies

$$\varepsilon \|w^\varepsilon\|_{L^2(\Gamma^\varepsilon)}^2 + \varepsilon \|\varepsilon \nabla_\Gamma w^\varepsilon\|_{L^2(\Gamma^\varepsilon)}^2 \leq C,$$

then there exists $w \in L^2(\Omega; H^1(\Gamma))$ such that as $\varepsilon \rightarrow 0$, up to a subsequence,

$$\begin{aligned} \mathcal{T}_\Gamma^\varepsilon(w^\varepsilon) &\rightharpoonup w && \text{weakly in } L^2(\Omega; H^1(\Gamma)), \\ \varepsilon \mathcal{T}_\Gamma^\varepsilon(\nabla_\Gamma w^\varepsilon) &\rightharpoonup \nabla_{\Gamma,y} w && \text{weakly in } L^2(\Omega \times \Gamma). \end{aligned}$$

Appendix C. Some details on the proof of Lemma 3.9. In the second equation in (3.1) and in equations (3.2), integrating by parts with respect to the time variable in the terms involving time derivatives, applying the periodic unfolding operator and the boundary unfolding operator, and using the properties of the unfolding operator, see e.g. (B.1), yields for $x \in \Omega$, $\tau \in (0, T]$

$$\begin{aligned} (C.1) \quad & -\langle \mathcal{T}^\varepsilon(c_i^\varepsilon), \partial_t \mathcal{T}^\varepsilon(\psi) \rangle_{Y_{i,\tau}} + \langle D_i(y) \nabla_y \mathcal{T}^\varepsilon(c_i^\varepsilon), \nabla_y \mathcal{T}^\varepsilon(\psi) \rangle_{Y_{i,\tau}} \\ & + \langle \mathcal{T}^\varepsilon(c_i^\varepsilon(\tau)), \mathcal{T}^\varepsilon(\psi(\tau)) \rangle_{Y_i} = \langle \mathcal{T}^\varepsilon(c_{i,0}^\varepsilon), \mathcal{T}^\varepsilon(\psi(0)) \rangle_{Y_i} \\ & + \langle F_i(\mathcal{T}^\varepsilon(c_i^\varepsilon)), \mathcal{T}^\varepsilon(\psi) \rangle_{Y_{i,\tau}} + \langle G_i(\mathcal{T}^\varepsilon(c_i^\varepsilon), \mathcal{T}^\varepsilon(p_a^\varepsilon)), \mathcal{T}^\varepsilon(\psi) \rangle_{\Gamma_\tau}, \\ (C.2) \quad & -\langle \mathcal{T}^\varepsilon(r_f^\varepsilon), \partial_t \mathcal{T}^\varepsilon(\varphi) \rangle_{\Gamma_\tau} + \langle D_f \nabla_{\Gamma,y} \mathcal{T}^\varepsilon(r_f^\varepsilon), \nabla_{\Gamma,y} \mathcal{T}^\varepsilon(\varphi) \rangle_{\Gamma_\tau} \\ & + \langle \mathcal{T}^\varepsilon(r_f^\varepsilon(\tau)), \mathcal{T}^\varepsilon(\varphi(\tau)) \rangle_\Gamma = \langle \mathcal{T}^\varepsilon(r_{f,0}^\varepsilon), \mathcal{T}^\varepsilon(\varphi(0)) \rangle_\Gamma - d_f \langle \mathcal{T}^\varepsilon(r_f^\varepsilon), \mathcal{T}^\varepsilon(\varphi) \rangle_{\Gamma_\tau} \\ & + \langle F_f(\mathcal{T}^\varepsilon(r_f^\varepsilon), \mathcal{T}^\varepsilon(r_b^\varepsilon)) - G_e(\mathcal{T}^\varepsilon(c_e^\varepsilon), \mathcal{T}^\varepsilon(r_f^\varepsilon), \mathcal{T}^\varepsilon(r_b^\varepsilon)), \mathcal{T}^\varepsilon(\varphi) \rangle_{\Gamma_\tau}, \\ & -\langle \mathcal{T}^\varepsilon(r_b^\varepsilon), \partial_t \mathcal{T}^\varepsilon(\varphi) \rangle_{\Gamma_\tau} + \langle D_b \nabla_{\Gamma,y} \mathcal{T}^\varepsilon(r_b^\varepsilon), \nabla_{\Gamma,y} \mathcal{T}^\varepsilon(\varphi) \rangle_{\Gamma_\tau} \\ & + \langle \mathcal{T}^\varepsilon(r_b^\varepsilon(\tau)), \mathcal{T}^\varepsilon(\varphi(\tau)) \rangle_\Gamma = \langle \mathcal{T}^\varepsilon(r_{b,0}^\varepsilon), \mathcal{T}^\varepsilon(\varphi(0)) \rangle_\Gamma - d_b \langle \mathcal{T}^\varepsilon(r_b^\varepsilon), \mathcal{T}^\varepsilon(\varphi) \rangle_{\Gamma_\tau} \\ & + \langle G_e(\mathcal{T}^\varepsilon(c_e^\varepsilon), \mathcal{T}^\varepsilon(r_f^\varepsilon), \mathcal{T}^\varepsilon(r_b^\varepsilon)) - G_d(\mathcal{T}^\varepsilon(r_b^\varepsilon), \mathcal{T}^\varepsilon(p_d^\varepsilon), \mathcal{T}^\varepsilon(p_a^\varepsilon)), \mathcal{T}^\varepsilon(\varphi) \rangle_{\Gamma_\tau}, \end{aligned}$$

and

$$\begin{aligned} (C.3) \quad & -\langle \mathcal{T}^\varepsilon(p_d^\varepsilon), \partial_t \mathcal{T}^\varepsilon(\varphi) \rangle_{\Gamma_\tau} + \langle D_d \nabla_{\Gamma,y} \mathcal{T}^\varepsilon(p_d^\varepsilon), \nabla_{\Gamma,y} \mathcal{T}^\varepsilon(\varphi) \rangle_{\Gamma_\tau} \\ & + \langle \mathcal{T}^\varepsilon(p_d^\varepsilon(\tau)), \mathcal{T}^\varepsilon(\varphi(\tau)) \rangle_\Gamma = \langle \mathcal{T}^\varepsilon(p_{d,0}^\varepsilon), \mathcal{T}^\varepsilon(\varphi(0)) \rangle_\Gamma - d_d \langle \mathcal{T}^\varepsilon(p_d^\varepsilon), \mathcal{T}^\varepsilon(\varphi) \rangle_{\Gamma_\tau} \\ & + \langle F_d(\mathcal{T}^\varepsilon(p_d^\varepsilon)) - G_d(\mathcal{T}^\varepsilon(r_b^\varepsilon), \mathcal{T}^\varepsilon(p_d^\varepsilon), \mathcal{T}^\varepsilon(p_a^\varepsilon)), \mathcal{T}^\varepsilon(\varphi) \rangle_{\Gamma_\tau}, \\ & -\langle \mathcal{T}^\varepsilon(p_a^\varepsilon), \partial_t \mathcal{T}^\varepsilon(\varphi) \rangle_{\Gamma_\tau} + \langle D_a \nabla_{\Gamma,y} \mathcal{T}^\varepsilon(p_a^\varepsilon), \nabla_{\Gamma,y} \mathcal{T}^\varepsilon(\varphi) \rangle_{\Gamma_\tau} \\ & + \langle \mathcal{T}^\varepsilon(p_a^\varepsilon(\tau)), \mathcal{T}^\varepsilon(\varphi(\tau)) \rangle_\Gamma = \langle \mathcal{T}^\varepsilon(p_{a,0}^\varepsilon), \mathcal{T}^\varepsilon(\varphi(0)) \rangle_\Gamma - d_a \langle \mathcal{T}^\varepsilon(p_a^\varepsilon), \mathcal{T}^\varepsilon(\varphi) \rangle_{\Gamma_\tau} \\ & + \langle G_d(\mathcal{T}^\varepsilon(r_b^\varepsilon), \mathcal{T}^\varepsilon(p_d^\varepsilon), \mathcal{T}^\varepsilon(p_a^\varepsilon)) - G_i(\mathcal{T}^\varepsilon(p_a^\varepsilon), \mathcal{T}^\varepsilon(c_i^\varepsilon)), \mathcal{T}^\varepsilon(\varphi) \rangle_{\Gamma_\tau}, \end{aligned}$$

where $\psi \in L^2(0, T; H^1(\Omega_i^\varepsilon))$ with $\partial_t \psi \in L^2(\Omega_{i,T}^\varepsilon)$ and $\varphi \in L^2(0, T; H^1(\Gamma^\varepsilon))$ with $\partial_t \varphi \in L^2(\Gamma_T^\varepsilon)$. Notice that the regularity of solutions of the microscopic problem implies $c_i^\varepsilon \in C([0, T]; L^2(\Omega_i^\varepsilon))$ and $r_j^\varepsilon, p_s^\varepsilon \in C([0, T]; L^2(\Gamma^\varepsilon))$, for $j = f, b$ and $s = a, d$.

Considering the sum of equations (C.1)-(C.3) with test functions $\psi(t, x) = 1$ in $\Omega_{i,T}^\varepsilon$ and $\varphi(t, x) = 1$ on Γ_T^ε , respectively, and using the nonnegativity of solutions, the structure of the reaction terms, and the assumptions on the initial data yields

$$\begin{aligned} (C.4) \quad & \|\mathcal{T}^\varepsilon(r_f^\varepsilon)(\tau, x, \cdot)\|_{L^1(\Gamma)} + \|\mathcal{T}^\varepsilon(r_b^\varepsilon)(\tau, x, \cdot)\|_{L^1(\Gamma)} + \|\mathcal{T}^\varepsilon(p_d^\varepsilon)(\tau, x, \cdot)\|_{L^1(\Gamma)} \\ & + 2\|\mathcal{T}^\varepsilon(p_a^\varepsilon)(\tau, x, \cdot)\|_{L^1(\Gamma)} + 2\|\mathcal{T}^\varepsilon(c_i^\varepsilon)(\tau, x, \cdot)\|_{L^1(Y_i)} \leq C_1 \|\mathcal{T}^\varepsilon(r_{f,0}^\varepsilon)(x, \cdot)\|_{L^1(\Gamma)} \\ & + \|\mathcal{T}^\varepsilon(r_{b,0}^\varepsilon)(x, \cdot)\|_{L^1(\Gamma)} + \|\mathcal{T}^\varepsilon(p_{d,0}^\varepsilon)(x, \cdot)\|_{L^1(\Gamma)} + 2\|\mathcal{T}^\varepsilon(p_{a,0}^\varepsilon)(x, \cdot)\|_{L^1(\Gamma)} \\ & + C_2 \|\mathcal{T}^\varepsilon(c_{i,0}^\varepsilon)(x, \cdot)\|_{L^1(Y_i)} + C_3 \leq C, \end{aligned}$$

for $\tau \in (0, T]$ and a.a. $x \in \Omega$.

The estimates in (3.15) are obtained by considering $\mathcal{T}^\varepsilon(c_i^\varepsilon)$ as a test function in (C.1), $\mathcal{T}^\varepsilon(r_f^\varepsilon)$ as a test function in the equation for $\mathcal{T}^\varepsilon(r_b^\varepsilon)$ and $\mathcal{T}^\varepsilon(r_b^\varepsilon) + \mathcal{T}^\varepsilon(r_f^\varepsilon)$ as a test function in the sum of equations for $\mathcal{T}^\varepsilon(r_b^\varepsilon)$ and $\mathcal{T}^\varepsilon(r_f^\varepsilon)$ in (C.2), $\mathcal{T}^\varepsilon(p_d^\varepsilon)$ as a test function in the equation for $\mathcal{T}^\varepsilon(p_d^\varepsilon)$ and $\mathcal{T}^\varepsilon(p_d^\varepsilon) + \mathcal{T}^\varepsilon(p_a^\varepsilon)$ as a test function in the sum of equations for $\mathcal{T}^\varepsilon(p_d^\varepsilon)$ and $\mathcal{T}^\varepsilon(p_a^\varepsilon)$ in (C.3), and by using the nonnegativity of solutions of the microscopic problem. To ensure that the time derivative is well-defined, we consider a standard approximation, using the Steklov average, of r_l^ε , p_s^ε , c_i^ε , for $l = f, b$ and $s = d, a$, i.e.

$$v^\zeta(t, x) = \frac{1}{\zeta} \int_{t-\zeta}^t \frac{1}{\zeta} \int_s^{s+\zeta} v(\sigma, x) d\sigma \kappa(s) ds,$$

with $\kappa(s) = 1$ for $s \in (0, T - \zeta)$ and $\kappa(s) = 0$ for $s \in [-\zeta, 0] \cup [T - \zeta, T]$, and then take $\zeta \rightarrow 0$, see e.g. [25] for more details.

To show boundedness of solutions of the microscopic problem we first consider $|\mathcal{T}^\varepsilon(r_f^\varepsilon)|^{p-1}$ for $p \geq 4$ as a test function in the first equation in (C.2) and using the nonnegativity of c_e^ε and r_f^ε and assumptions on the nonlinear function F_f we obtain

$$\begin{aligned} (C.5) \quad & \|\mathcal{T}^\varepsilon(r_f^\varepsilon)(\tau)\|_{L^p(\Gamma)}^p + 4 \frac{p-1}{p} \|\nabla_{\Gamma, y} |\mathcal{T}^\varepsilon(r_f^\varepsilon)|^{\frac{p}{2}}\|_{L^2(\Gamma_\tau)}^2 \\ & \leq C_1 p \left[1 + \|\mathcal{T}^\varepsilon(r_f^\varepsilon)\|_{L^p(\Gamma_\tau)}^p \right] + C_2 p \langle \mathcal{T}^\varepsilon(r_b^\varepsilon), |\mathcal{T}^\varepsilon(r_f^\varepsilon)|^{p-1} \rangle_{\Gamma_\tau}. \end{aligned}$$

Applying the Hölder inequality and inequalities in (3.18), the last term in (C.5) is estimated in the following way

$$\begin{aligned} (C.6) \quad & \langle \mathcal{T}^\varepsilon(r_b^\varepsilon), |\mathcal{T}^\varepsilon(r_f^\varepsilon)|^{p-1} \rangle_{\Gamma_\tau} \leq \frac{1}{p} \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^4(\Gamma_\tau)}^p \\ & + C_1 \frac{p-1}{p} \|\nabla_{\Gamma, y} |\mathcal{T}^\varepsilon(r_f^\varepsilon)|^{\frac{p}{2}}\|_{L^2(\Gamma_\tau)}^2 \|\mathcal{T}^\varepsilon(r_f^\varepsilon)|^{\frac{p}{2}}\|_{L^4(0, \tau; L^2(\Gamma))}^4 \\ & \leq \frac{1}{p} \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^4(\Gamma_\tau)}^p + C_2 \frac{p-1}{p} \|\nabla_{\Gamma, y} |\mathcal{T}^\varepsilon(r_f^\varepsilon)|^{\frac{p}{2}}\|_{L^2(\Gamma_\tau)}^2 \times \\ & \quad \times \left[\int_0^\tau \|\nabla_{\Gamma, y} |\mathcal{T}^\varepsilon(r_f^\varepsilon)|^{\frac{p}{2}}\|_{L^2(\Gamma)}^2 \|\mathcal{T}^\varepsilon(r_f^\varepsilon)|^{\frac{p}{2}}\|_{L^1(\Gamma)}^2 dt \right]^{\frac{1}{4}} \leq \frac{1}{p} \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^4(\Gamma_\tau)}^p \\ & + C_2 \frac{p-1}{p} \|\nabla_{\Gamma, y} |\mathcal{T}^\varepsilon(r_f^\varepsilon)|^{\frac{p}{2}}\|_{L^2(\Gamma_\tau)}^2 \sup_{(0, \tau)} \|\mathcal{T}^\varepsilon(r_f^\varepsilon)|^{\frac{p}{2}}\|_{L^1(\Gamma)}^{\frac{1}{2}} \leq \frac{1}{p} \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^4(\Gamma_\tau)}^p \\ & + \delta \frac{p-1}{p^2} \|\nabla_{\Gamma, y} |\mathcal{T}^\varepsilon(r_f^\varepsilon)|^{\frac{p}{2}}\|_{L^2(\Gamma_\tau)}^2 + C_\delta p^3 \sup_{(0, \tau)} \|\mathcal{T}^\varepsilon(r_f^\varepsilon)|^{\frac{p}{2}}\|_{L^1(\Gamma)}^2, \end{aligned}$$

for $\tau \in (0, T]$ and $x \in \Omega$. Using the Gagliardo-Nirenberg inequality, see (3.18), we also obtain

$$(C.7) \quad \|\mathcal{T}^\varepsilon(r_f^\varepsilon)\|_{L^p(\Gamma_\tau)}^p \leq \delta \frac{p-1}{p^2} \|\nabla_{\Gamma, y} |\mathcal{T}^\varepsilon(r_f^\varepsilon)|^{\frac{p}{2}}\|_{L^2(\Gamma_\tau)}^2 + C_\delta p \sup_{(0, \tau)} \|\mathcal{T}^\varepsilon(r_f^\varepsilon)|^{\frac{p}{2}}\|_{L^1(\Gamma)}^2,$$

for $\tau \in (0, T]$ and $x \in \Omega$. Then using estimates (C.6) and (C.7) in (C.5) yields inequality (3.21).

To show boundedness of c_e^ε we consider $|c_e^\varepsilon|^{p-1}$, for $p \geq 4$, as a test function in the first equation in (3.1) and, using the assumptions on F_e and the nonnegativity of

r_f^ε and c_e^ε we obtain

$$(C.8) \quad \|c_e^\varepsilon(\tau)\|_{L^p(\Omega_\varepsilon)}^p + 4\frac{p-1}{p}\|\nabla_{\Gamma,y}|c_d^\varepsilon|^{\frac{p}{2}}\|_{L^2(\Omega_{\varepsilon,\tau}^\varepsilon)}^2 \leq C_1 p \left[1 + \|c_e^\varepsilon\|_{L^p(\Omega_{\varepsilon,\tau}^\varepsilon)}^p\right] \\ + C_2 p \varepsilon \langle r_b^\varepsilon, |c_e^\varepsilon|^{p-1} \rangle_{\Gamma_\tau^\varepsilon}.$$

The last term in (C.8) can be estimated in the following way

$$(C.9) \quad \varepsilon |Y| \langle r_b^\varepsilon, |c_e^\varepsilon|^{p-1} \rangle_{\Gamma_\tau^\varepsilon} = \langle \mathcal{T}^\varepsilon(r_b^\varepsilon), |\mathcal{T}^\varepsilon(c_e^\varepsilon)|^{p-1} \rangle_{\Omega_\tau \times \Gamma} \\ \leq \int_{\Omega_\tau} \left[\int_\Gamma |\mathcal{T}^\varepsilon(c_e^\varepsilon)|^{\frac{4(p-1)}{3}} d\sigma_y \right]^{\frac{3}{4}} \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^4(\Gamma)} dx dt \\ \leq \frac{p-1}{p} \int_{\Omega_\tau} \left[\int_\Gamma (|\mathcal{T}^\varepsilon(c_e^\varepsilon)|^{\frac{p}{2}})^{\frac{8}{3}} d\sigma_y \right]^{\frac{3}{4}} dx dt + \frac{1}{p} \int_{\Omega_\tau} \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^4(\Gamma)}^p dx dt.$$

Applying the trace inequality (A.1) to $|\mathcal{T}^\varepsilon(c_e^\varepsilon)|^{\frac{p}{2}}$ and using the properties of the unfolding operator \mathcal{T}^ε , see e.g. (B.1), the first term on the right-hand side of (C.9) is estimated as

$$\| |\mathcal{T}^\varepsilon(c_e^\varepsilon)|^{\frac{p}{2}} \|_{L^2(\Omega_\tau; L^{8/3}(\Gamma))}^2 \leq \frac{\delta}{p} \|\nabla_y |\mathcal{T}^\varepsilon(c_e^\varepsilon)|^{\frac{p}{2}}\|_{L^2(\Omega_\tau; L^2(Y_e))}^2 \\ + C_\delta p^3 \| |\mathcal{T}^\varepsilon(c_e^\varepsilon)|^{\frac{p}{2}} \|_{L^2(\Omega_\tau; L^2(Y_e))}^2 \leq |Y| \left[C_\delta p^3 \|c_e^\varepsilon\|_{L^p(\Omega_{\varepsilon,\tau}^\varepsilon)}^p + \frac{\delta}{p} \varepsilon^2 \|\nabla |c_e^\varepsilon|^{\frac{p}{2}}\|_{L^2(\Omega_{\varepsilon,\tau}^\varepsilon)}^2 \right].$$

To estimate $\|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^p(\Omega_\tau; L^4(\Gamma))}$ we consider $|\mathcal{T}^\varepsilon(r_b^\varepsilon)|^3$ as a test functions in the second equation in (C.2) and obtain

$$(C.10) \quad \|\mathcal{T}^\varepsilon(r_b^\varepsilon)(\tau)\|_{L^4(\Gamma)}^4 + \|\nabla_{\Gamma,y} |\mathcal{T}^\varepsilon(r_b^\varepsilon)|^2\|_{L^2(\Gamma_\tau)}^2 \leq \|\mathcal{T}^\varepsilon(r_{b0}^\varepsilon)\|_{L^4(\Gamma_\tau)}^4 \\ + C_1 \langle \mathcal{T}^\varepsilon(p_a^\varepsilon), |\mathcal{T}^\varepsilon(r_b^\varepsilon)|^3 \rangle_{\Gamma_\tau} + C_2 \langle \mathcal{T}^\varepsilon(r_f^\varepsilon) \mathcal{T}^\varepsilon(c_e^\varepsilon), |\mathcal{T}^\varepsilon(r_b^\varepsilon)|^3 \rangle_{\Gamma_\tau},$$

for $x \in \Omega$ and $\tau \in (0, T]$. Applying the Gagliardo-Nirenberg inequality

$$\|v\|_{L^3(\Gamma)} \leq C_1 \|\nabla_{\Gamma,y} v\|_{L^2(\Gamma)}^{2/3} \|v\|_{L^1(\Gamma)}^{1/3}$$

to $|\mathcal{T}^\varepsilon(r_b^\varepsilon)|^2$ and using the estimates in (3.16) yield

$$|\langle \mathcal{T}^\varepsilon(p_a^\varepsilon), |\mathcal{T}^\varepsilon(r_b^\varepsilon)|^3 \rangle_{\Gamma_\tau}| \leq \delta \|\nabla_{\Gamma,y} |\mathcal{T}^\varepsilon(r_b^\varepsilon)|^2\|_{L^2(\Gamma_\tau)}^2 \sup_{(0,\tau)} \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^2(\Gamma)} \\ + \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^6(0,\tau; L^2(\Gamma))}^6 + C_\delta \|\mathcal{T}^\varepsilon(p_a^\varepsilon)\|_{L^2(\Gamma_\tau)}^2 \leq C_1 \delta \|\nabla_{\Gamma,y} |\mathcal{T}^\varepsilon(r_b^\varepsilon)|^2\|_{L^2(\Gamma_\tau)}^2 + C_2,$$

for $\tau \in (0, T]$ and $x \in \Omega$. The boundedness of $\mathcal{T}^\varepsilon(r_f^\varepsilon)$, see (3.22), ensures

$$|\langle \mathcal{T}^\varepsilon(r_f^\varepsilon) \mathcal{T}^\varepsilon(c_e^\varepsilon), |\mathcal{T}^\varepsilon(r_b^\varepsilon)|^3 \rangle_{\Gamma_\tau}| \leq C_1 \|\mathcal{T}^\varepsilon(c_e^\varepsilon)\|_{L^p(\Gamma_\tau)} \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^{\frac{3p}{p-1}}(\Gamma_\tau)}^3 \\ \leq C_2 \left[\|\mathcal{T}^\varepsilon(c_e^\varepsilon)\|_{L^p(\Gamma_\tau)}^4 + \|\mathcal{T}^\varepsilon(r_b^\varepsilon)\|_{L^4(\Gamma_\tau)}^4 \right],$$

for $p \geq 4$. Then combining the estimates above and using Gronwall's inequality in (C.10) implies

$$(C.11) \quad \|\mathcal{T}^\varepsilon(r_b^\varepsilon)(\tau)\|_{L^4(\Gamma)} + \|\nabla_{\Gamma,y} |\mathcal{T}^\varepsilon(r_b^\varepsilon)|^2\|_{L^2(\Gamma_\tau)}^{\frac{1}{2}} \leq C_1 [1 + \|\mathcal{T}^\varepsilon(c_e^\varepsilon)\|_{L^p(\Gamma_\tau)}],$$

for $\tau \in (0, T]$, $x \in \Omega$, and $p \geq 4$. Hence using (C.11) in (C.9) and applying the relations between the original and unfolded sequences, see (B.1), estimate (C.8) yields

$$(C.12) \quad \begin{aligned} \| |c_e^\varepsilon(\tau)|^{\frac{p}{2}} \|_{L^2(\Omega_e^\varepsilon)}^2 + 4 \frac{p-1}{p} \| \nabla |c_e^\varepsilon|^{\frac{p}{2}} \|_{L^2(\Omega_{e,\tau}^\varepsilon)}^2 &\leq \delta_1 \frac{p-1}{p} \| \nabla |c_e^\varepsilon|^{\frac{p}{2}} \|_{L^2(\Omega_{e,\tau}^\varepsilon)}^2 \\ &\quad + C_\delta p^3 (1 + \|c_e^\varepsilon\|_{L^p(\Omega_{e,\tau}^\varepsilon)}^p) + C_1 (1 + \varepsilon \|c_e^\varepsilon\|_{L^p(\Gamma_\tau^\varepsilon)}^p). \end{aligned}$$

Notice that the Gagliardo-Nirenberg inequality and the properties of an extension $|\bar{c}_e^\varepsilon|^{\frac{p}{2}}$ of $|c_e^\varepsilon|^{\frac{p}{2}}$ from Ω_e^ε into Ω , see (3.4), ensures

$$(C.13) \quad \begin{aligned} \|c_e^\varepsilon\|_{L^p(\Omega_{e,\tau}^\varepsilon)}^p &\leq \| |\bar{c}_e^\varepsilon|^{\frac{p}{2}} \|_{L^2(\Omega_\tau)}^2 \leq \mu_1 \int_0^\tau \| |\bar{c}_e^\varepsilon|^{\frac{p}{2}} \|_{L^1(\Omega)}^{4/5} \| \nabla |\bar{c}_e^\varepsilon|^{\frac{p}{2}} \|_{L^2(\Omega)}^{6/5} dt \\ &\leq \frac{\delta_1}{p^3} \| \nabla |\bar{c}_e^\varepsilon|^{\frac{p}{2}} \|_{L^2(\Omega_\tau)}^2 + C_{\delta,1} p^{\frac{9}{2}} \sup_{(0,\tau)} \| |\bar{c}_e^\varepsilon|^{\frac{p}{2}} \|_{L^1(\Omega)}^2 \\ &\leq \frac{\delta}{p^3} \| \nabla |c_e^\varepsilon|^{\frac{p}{2}} \|_{L^2(\Omega_{e,\tau}^\varepsilon)}^2 + C_\delta p^{\frac{9}{2}} \sup_{(0,\tau)} \| |c_e^\varepsilon|^{\frac{p}{2}} \|_{L^1(\Omega_e^\varepsilon)}^2. \end{aligned}$$

Then applying trace inequality (3.3) in the last term in (C.12) and using the estimate (C.13) yield (3.26).